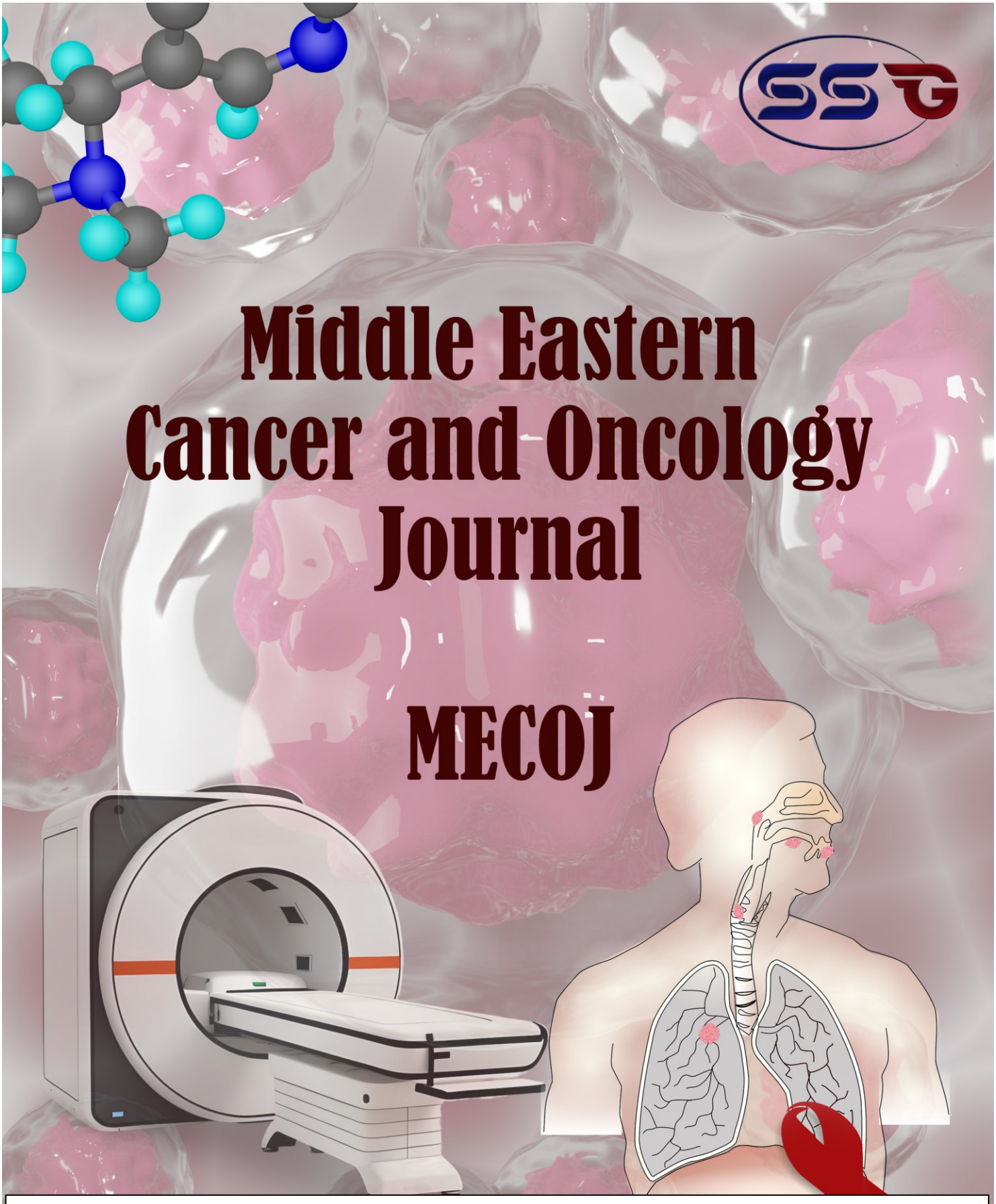

Middle Eastern Cancer and Oncology Journal

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Volume 1 – Issue 1

The “Middle Eastern Cancer and Oncology Journal (MECOJ)” is an online, peer-reviewed, open access journal that strives to push the boundaries of oncology by enhancing the understanding of cancer biology, evolving treatment methods, and effective prevention strategies. It is established in 2025 by OncoEval Pioneers Group and owned by Scientific Steps International Publishing Services which owns the copyright and licensing for all issues and articles in the journal. MECOJ serves as a critical platform for the swift publication of pioneering research that connects the intricate scientific findings with tangible clinical applications. The journal champions the exploration of innovative therapeutic approaches and groundbreaking genetic discoveries that redefine cancer care standards globally. Emphasizing both regional challenges in the Middle East and global advancements, the journal aims to foster collaborative insights that enhance cancer research and treatment outcomes worldwide.

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Editorial letter!

We are pleased to welcome you to the Middle Eastern Cancer and Oncology Journal (MECOJ), a peer-reviewed, open-access journal committed to advancing the field of oncology through high-quality research and scientific discourse. Established in 2025 by OncoEval Pioneers Group and owned by Scientific Steps International Publishing Services, MECOJ aims to bridge the gap between scientific innovation and clinical application, fostering a deeper understanding of cancer biology, cutting-edge treatment modalities, and effective prevention strategies.

Our mission is to serve as a dynamic platform for the swift dissemination of pioneering research that connects intricate scientific discoveries with real-world medical applications. MECOJ is dedicated to the exploration of novel therapeutic approaches, emerging genetic insights, and evolving oncological care standards that redefine cancer treatment globally. While we emphasize challenges specific to the Middle East, our scope remains global, facilitating international collaborations that enhance cancer research and treatment outcomes worldwide.

MECOJ is published quarterly, ensuring a meticulous peer-review process that upholds the highest standards of academic integrity. We welcome original research articles, case reports, and review articles, all published in English, across a wide spectrum of oncology-related topics. Our peer-review process is designed to be both rigorous and efficient, typically taking 30 to 60 days from submission to decision. As the journal continues to grow, we anticipate increasing the frequency of publication to accommodate the expanding volume of high-quality submissions.

We take pride in our journal's recognition by the Iraqi Society of Clinical Oncology (ISCO), reflecting our commitment to excellence and our engagement with leading oncological research communities. We invite researchers, clinicians, and academics to contribute to their work and join us in shaping the future of cancer research and treatment.

Thank you for your support and contributions to MECOJ. We look forward to fostering meaningful scientific advancements in oncology.

Editorial Board

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Review Article

Medicinal Plants Commonly Used Against Cancer and Human Immunodeficiency Virus in Malaysia

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Abstract

Human immunodeficiency virus (HIV) and cancer are both considered life-threatening diseases that impose a significant global burden. Despite significant advancements in the treatment and management of both cancer and HIV, challenges persist. However, challenges such as drug resistance, limited accessibility in low-resource settings, and a paucity of cost-effective alternatives persist, underscoring the need for continued research. Chemotherapy frequently results in severe toxicities, including myelosuppression and organ damage, while antiretroviral treatments can lead to long-term adverse effects such as metabolic disorders and liver toxicity. Conversely, natural therapies, encompassing the utilization of plant-derived products in cancer and HIV treatment, have emerged as a potential avenue to mitigate adverse side effects. The utilization of natural products has demonstrated consistent efficacy in the prevention of HIV and cancer. The development of anti-HIV/cancer products has incorporated natural plants and extracts. Indigenous communities have utilized traditional herbal medicine for the treatment of various diseases, including HIV and cancer. A number of Malaysian plants have been identified as having significant anti-HIV/cancer properties, and some of the commonly used plants are described in this review with an account of their compounds and modes of action. However, to date, only a limited number of Malaysian plants have been subjected to bioactivity testing, highlighting the necessity for further research to fully elucidate their medicinal potential and inform the development of novel therapeutic interventions for combating HIV/cancer.

Keywords: *Anti-Cancer, Anti-HIV, Medicinal Plants, Phytotherapy, Traditional Medicine, Natural Compounds.*

Maya Aljindy

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Introduction

Cancer and HIV are the leading causes of death worldwide (Siegel et al., 2016). Despite the implementation of extensive awareness campaigns emphasizing the methods of prevention, treatment, and management of these diseases, they continue to account for a substantial proportion of mortalities in comparison to other diseases. This phenomenon contributes to a decline in overall quality of life and a substantial number of fatalities. While significant advancements have been made in the treatment of both HIV and cancer, the need for alternative sustainable, more accessible, and more affordable methods of prevention and treatment remains paramount to reduce the mortality rate from these diseases. This approach involves the utilization and maintenance of natural methods and therapies derived from indigenous knowledge, encompassing herbs, spices, plants, trees, and vegetables (Mohammed, 2019).

The likelihood of developing cancer is associated with detrimental lifestyle habits, such as sedentary living, a diet high in processed foods, and excessive smoking and alcohol consumption (Waks & Winer, 2019). Additional factors contributing to cancer development include excessive sun exposure and interaction with harmful chemicals. In some cases, the onset of cancer is age-related. Given the wide spectrum of conditions under which cancer can be contracted, it is essential to have measures to proactively prevent infection, while effectively treating and managing the infected parties (Corcoran & Chabner, 2018).

Cancer treatment has historically involved a variety of methodologies, including chemotherapy, immunotherapy, targeted therapy, and hormone therapy, as well as surgical interventions aimed at extirpating cancerous lesions (Anghileri & Robert, 2019). The employment of pharmaceutical agents has been a central tenet of these therapeutic approaches, with the aim of reducing tumor size, eradicating malignancies, or halting their progression. However, the extensive use of pharmaceuticals in cancer treatment has been associated with adverse effects, including toxicity, which can lead to fatalities (Anghileri & Robert, 2019). Consequently, there have been clinical studies and advancements in plant-derived anti-cancer drugs for clinical use. The objective of these studies is to measure the effectiveness of these plant-derived drugs in comparison to existing pharmaceuticals. A key metric of efficacy would be the reduction in mortality rates due to toxicity, as chemotherapy is known to carry a high burden of adverse side effects (Choudhari et al., 2020).

Furthermore, HIV is an acquired viral disease that attacks the human immune system, weakening CD4 cells, which are useful for fighting infections in the body, thereby rendering the body incompetent in warding off infections and cancers (Chinsembu, 2016). HIV is most treated through diverse drug regimens, which are uniformly called antiretroviral therapy (ART). This therapy consists of taking multiple tablets daily, which prevents the viral load from multiplying. A reduced viral load leads to a less aggressive progression of HIV to AIDS, thereby enhancing the health and lifespan of infected individuals (Abdel-Kader et al., 2018). The efficacy of ART is contingent on its daily and precise administration. Inconsistent adherence to ART has been observed to result in viral load multiplication. This has led to challenges in low- and middle-income countries, where the health delivery system often lacks the capacity to meet the demand for HIV medications (Akram et al., 2018). Consequently, there has been a growing interest in exploring natural and plant-based remedies for HIV prevention and treatment. These methods of treatment are considered more favourable due to their sustainability and the reduced adverse effects they impose on infected patients. Consequently, this has contributed to the accelerated development and clinical implementation of anti-HIV drugs derived from plants (Adana et al., 2018).

It has been noted that both cancer and HIV present challenges in treatment that are analogous, including drug resistance, adverse side effects from existing therapies, and disparities in healthcare access. Furthermore, the growing interest in plant-derived compounds for both diseases highlights a shared opportunity to explore sustainable and less toxic alternatives that address these gaps.

Medicinal plants play a pivotal role in communities' treatment of diseases due to their accessibility, which facilitates prompt provision of necessary medicine to patients within the vicinity. While medicinal plants may possess reduced potency, they exhibit reduced toxicity, thereby minimizing the likelihood of adverse side effects in patients (Mohammed, 2019). Compared to synthetic counterparts, natural medicines have demonstrated enhanced efficacy in treating diseases. Furthermore, the affordability of medicinal plants ensures enhanced accessibility, thereby expanding treatment options to a greater number of individuals compared to synthetic medicine, which is often more expensive. These characteristics position the utilization of plants in medicine as a beneficial, effective, and holistic approach to healthcare (Nisar et al., 2018).

Malaysia is distinguished by its extensive biodiversity, as evidenced by its habitat for over 23,000 plant species. This substantial reserve of flora offers a valuable resource for investigating the medicinal properties of these organisms (Zaki et al., 2019). The objective of this review is to examine the anti-cancer and anti-HIV properties of select Malaysian plants.

Plant-Derived Anti-Cancer Agents in Clinical Use

The anticancer properties of plants have been recognized in clinical procedures for years, with approximately two-thirds of anti-cancer drugs originating from plants (Sak, 2012). Anti-cancer agents are described as chemicals that weaken cancer cells by either killing them or reducing their multiplication. There are several plant-derived anti-cancer agents that have been successfully implemented in clinical use due to their chemoprotective effects. The National Cancer Institute (NCI) has conducted extensive research, examining over 35,000 plants and identifying potential anti-cancer properties in approximately 3,000 of them (Shalabi et al., 2015). **Figure 1** illustrates some of the anti-cancer drugs derived from plants (Kuruppu et al., 2019).The World Health Organization acknowledges plants as a vital contributor to achieving global healthcare objectives. Herbs and plants have been recognized for their medicinal value and have been used in Europe and the Middle East. Studies in these regions have influenced other parts of the world, prompting the strong consideration of plant-derived agents for the prevention and cure of cancer (Bahadur et al., 2020).

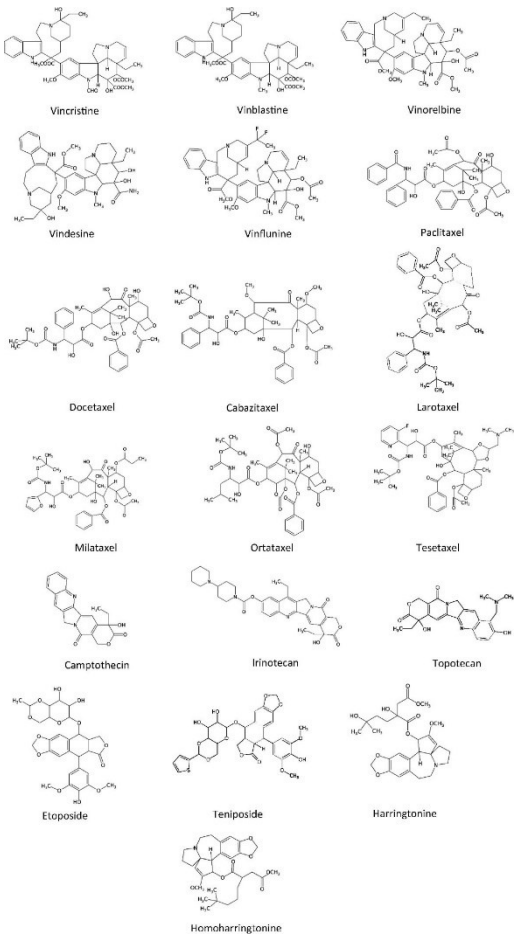

Figure 1. Chemical Structures of Anti-Cancer Drugs Derived from Plants That are in Clinical Use (X. Wang et al., 2018).

The utilization of plants in cancer prevention is driven by the necessity to reverse the adverse effects of chemotherapy and enhance the survival rates of patients' post-surgery. The efficacy of plant-derived cancer agents in impeding cancer cell proliferation in specific bodily regions has been demonstrated (Zaid et al., 2012). For instance, the onion plant Allium cepa L has been found to be effective in inhibiting the growth of breast cancer cells by blocking the accumulation of fatty acids in the adipose tissues (Y. Wang et al., 2012). Another in vitro study also observed the anti-tumor effect of the aloe vera plant in both breast and cervical carcinoma cell lines (HeLa). The study's findings indicated that exposure to aloe vera compounds led to the death of cancerous cells, while having no effect on normal cells (Ahmed & Husain, 2014).

The incorporation of flora, namely plants, herbs, and vegetables, into an individual's dietary regimen has been demonstrated to exert a substantial influence on the probability of contracting cancer, in comparison to an individual with an inadequate diet. Ahmad et al. (2017) posit that in the nascent stages of cancer, it is feasible to arrest its progression, impeding its dissemination to other cells and halting its growth (Ahmad et al., 2017). This assertion is supported by the findings of Aung et al. (2017), who discovered that Calligonum Comosum extracts exert a substantial impact on the latency of hepatocellular carcinoma cells. The use of herbal-based medicines has been proposed as a highly effective cancer prevention strategy due to their potential to mitigate the likelihood of drug interactions, which can compromise the efficacy of combination therapy in addressing cancerous conditions. In comparison to synthetic anti-cancer drugs, natural options are often more cost-effective, readily available, straightforward in formulation, and characterized by a low incidence of adverse side effects (Ahmad et al., 2017).

Malaysian Plants that Have Anti-Cancer Properties

In Malaysia, the primary focus on herbal remedies and plant-based treatments for cancer prevention and treatment is largely driven by the country's abundant rainforests (Mainasara et al., 2018). Local communities have traditionally utilized potent herbs in the treatment of minor malignancies, and at the pharmaceutical level, there has been a growing incorporation of herbal and plant-extract based medications in cancer treatment (Rahman, 2016). While most of the plants identified as having anti-cancer properties have yet to be fully commercialized, they have been effectively used in treating cancer patients with success (Hashim et al., 2016). The combination of plant-derived anti-cancer drugs has been shown to reduce the likelihood of drug resistance in patients. This is due to the plant extracts' capacity to impede ATP binding cassette (ABC) transporters in conjunction with multidrug resistance

proteins (MRP-s), thereby enhancing the efficacy of treatment in patients (Shabani, 2016). A multitude of studies have identified the chemoprotective and anticarcinogenic properties of plants in the treatment of cancer, a subject that will be addressed in the ensuing discussion.

Goniothalamus Umbrosus

The Kenerak plant (G. umbrosus) is a species of plant that is native to Malaysia. It has been utilized in the field of pharmaceuticals for its benefits in maternal health care and general wellbeing. However, research has identified specific species of this plant that contain styryl-lactones and acetogenins, which have been shown to have toxic effects on various forms of cancer, including colon, breast, pancreas, and kidney cancers (Ghazali et al., 2016).

Furthermore, styryl-lactones from the G. umbrosus species have been identified as effective inducers of apoptosis in mammalian and cancer cells (Arbyn et al., 2020). Ethyl acetate, a compound derived from the G. umbrosus plant, has demonstrated significant potential in the inhibition of cancer growth and spread in breast cancer cells (MCF7) (Arbyn et al., 2020). Following treatment with this compound, a mortality of the cancer cells in the breast was observed. Consequently, there has been a surge in research endeavors exploring the potential of employing plant extracts in the treatment of breast cancer (Ibrahim et al., 2019).

Typhonium Flagelliforme

In Malaysia, the plant is referred to as Keladi Tikus, and it is employed as a derivative drug for the treatment of various forms of cancer. This herbaceous plant, which often grows up to 30 centimeters in height, is utilized as a medicinal agent. The plant's juice is orally administered after the entire plant is crushed (Setiawati et al., 2016). In vitro studies have demonstrated the efficacy of an extract of Typhonium flagelliforme in treating NCI-H23 human lung carcinoma, T-47D human breast carcinoma cell lines, and P388 murine leukemia cells (Setiawati et al., 2016). Moreover, the plant extract has been utilized in Malaysia for the treatment of malignancies.Notwithstanding the plant's anti-cancer properties, clinical trials have been stagnant. The stem and leaves of this tuber plant have been found to contain more potent anti-cancer agents (Sianipar & Purnamaningsih, 2018).

Clinacanthus Nutans

The plant is known in the local context as Sabah snake grass in Malaysia, and it is classified within the family of Acanthaceae (Alam et al., 2016). It is regarded as one of the most ancient native herbs, originating from tropical Asia. It is utilized as a conventional treatment agent in Malaysia, China, and Thailand (Ghantous & Abu Elnaaj, 2017). The plant has been employed to treat various ailments, including animal bites, skin irritations, diabetes, and the Herpes simplex virus (HSV). However, studies have demonstrated that the chloroform extracts from this plant exhibit potent effects in destroying anti-cancer cells in vitro, including HepG2, IMR32, NCL-H23, SNU-1, HeLa, LS-174T, K562, and Raji cells (Ng et al., 2017). Furthermore, the leaves of this plant have been shown to possess significant antiviral and anti-inflammatory properties (Teoh et al., 2017). In addition, they have been identified as effective in inhibiting neutrophil response and the formation of edema. Emerging evidence suggests that C. nutans holds significant anti-tumorigenic effects, which are vital components of anti-cancer growth (Huang et al., 2015). Studies have indicated that the chloroform extract of C. nutans leaves is a potent agent capable of eliminating free radicals and preventing the growth of cancerous cells in culture. Yakop et al. (2018) further suggested that these agents could serve as an effective alternative to chemotherapy for individuals at risk of developing cancer.

Plant-Derived Anti-HIV Agents in Clinical Use

Plants are increasingly being recognized as effective in the development of anti-HIV agents based on their diverse medicinal value. While there are still limited studies to discuss plants that prevent one from being infected with HIV, there is evidence that the inclusion of medicinal herbs and plants help in patients who have drug resistance, toxicity, and other co-morbidities. For example, when an HIV-positive patient eats organic foods, their immune system is strengthened and they have fewer health complications (Prinsloo et al., 2018).

It is common for HIV patients to have liver and kidney toxicity. However, when these patients took herbal medicines and herbs, they were able to get rid of the side effects of toxicity. There was an improvement in their liver and kidney health (Khan, 2017).

Adansonia digitata, Terminalia sericea, Hypoxis Hemerocallidea, and Moringa oleifera have been shown to inhibit HIV-1 reverse transcriptase. HIV patients who used these medicinal plants as a complementary therapy to their HIV treatment regimen were found to have a lower viral load and an increase in their CD4 count (Habibi et al., 2019). However, it is important to note that there has been resistance in several countries to the full adoption of herbal medicine for the treatment of HIV. A common reason for this is that there is still ongoing research into how the medicinal plants would interact with synthetic drugs and whether there would be any side effects (Jayasundar et al., 2019).

Plants are also used to treat opportunistic infections that are common in patients infected with HIV/AIDS. The opportunistic infections include cancer,

tuberculosis, skin and oral infections, and these are effectively treated with plants and herbs in HIV patients. The Moringa plant is commonly used to treat respiratory infections in HIV patients. It contains a similar structure to nucleoside analogues found in synthetic antiretroviral drugs (Kurapati et al., 2016).

Secondary symptoms of HIV/AIDS are also effectively managed through the consistent use of medicinal plants and herbs. This is seen in the case of tobacco plants, which produce monoclonal antibodies that are essential for supporting the compromised immune system of HIV patients. Since the disease affects and weakens the immune system, the plants used would contain high nutritional and pharmaceutical value (Okay & Sezgin, 2018).

Natural products that have been discovered to contain significant anti-HIV compounds include calanolides (coumarins), ursolic and betulinic acids (triterpenes), baicalin (flavonoid), polycitone A (alkaloid), and lithospermic acid (phenolic compound). However, they are all still in clinical trials and have not yet been commercialized. These plant-derived drugs have been found to have similar structures within the nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes (Boukandou Mounanga et al., 2018).

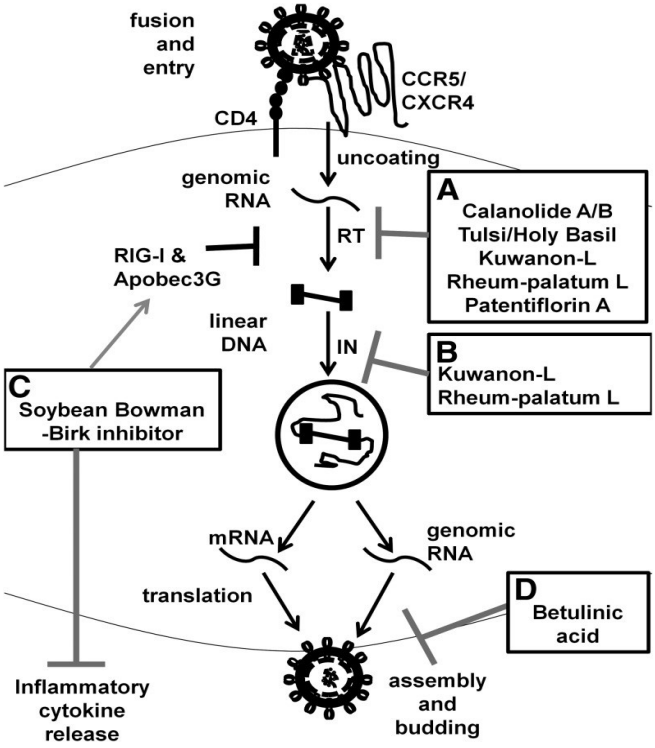

Figure 2. Plants and Compounds Used in HIV Suppression (Cary & Peterlin, 2018)

Figure 2 shows a summary of the plants used to suppress HIV replication. The compounds derived from the plants are also shown, indicating the role they play in the life cycle of the HIV virus. The inclusion of plant-derived anti-HIV agents focuses primarily on the suppression of the virus. These inhibitory agents are effective in targeting mutant cells, suppressing viral replication, and proving to be a cost-effective alternative to ART (Chaturonrutsamee et al., 2018; Okay & Sezgin, 2018).

Malaysian Plants that Have Anti-HIV Properties

Rainforest climates such as Malaysia are typically known for having a wide variety of pharmaceutically useful plants. The following plants have been identified as derivatives for anti-HIV drugs:

Calophyllum

The Calophyllum tree was first discovered in 1987 on the island of Borneo in Malaysia. The National Cancer Institute (NCI) led an expedition to find a cancer cure in the rainforests but instead discovered that the Calophyllum tree had anti-HIV properties. It was discovered that several compounds could be extracted from the tree that were pharmaceutically useful for the purpose of preventing HIV. The part that is harvested is the fruit and the branches from which the compound Calanolide A is derived. The other compounds derived from this plant are dihydrocostatolide and cordatolide A/B, dipyranocoumarins, and soulattrolide. These compounds were found to be able to inhibit the activity of viral infection of T cells in HIV patients (Lim et al., 2016).

Calanolide A

This compound is extracted from Calophyllum lanigerum var austrocoriaceum, an unusual member of the Guttiferae or mangosteen family (Wu et al., 2017). In vitro studies have shown that calanolide A, a non-nucleoside reverse transcriptase inhibitor, may be useful in HIV prevention. It was found to be effective in inhibiting cells from being infected by the virus, even those strains that had failed other drugs such as zidovudine (AZT) and nevirapine. The studies showed that the drug would work optimally when combined with other inhibitors such as AZT, didanosine, nevirapine and carbovir. This compound works by crossing the blood-brain barrier and accumulating in the lymph nodes. A modified and more potent structure of calanolide, F18, was discovered in 2017 (Pawar & Patil, 2019).

Calophyllum Teysmannii Var. Inophylloide

This plant, also discovered in the Borneo Islands of Malaysia, has been shown to have anti-HIV properties. The latex of this tree produces the compound costatolide, also called calanolide B, which also shows activity against HIV. Both compounds are classified as non-nucleoside reverse transcriptase inhibitors

(NNRTIs). These drugs protect and prevent the healthy T-cells in the body from being infected by the HIV virus (Kainuma et al., 2016). When comparing the two plants from Malaysia, it was found that even the latex of Calophyllum teysmanii produces (-)-calanolide B (70), which is less potent than the (+)-calanolide A of Calophyllum lanigerum, but it is a more sustainable option as it is derived from the latex of the tree, eliminating the need to cut down the tree (Jain et al., 2018).

The processing of these drugs has been spearheaded by Sarawak Medichem Pharmaceuticals, a collaboration between the Sarawak state government and Medichem Research, Inc. However, the commercialization of these drugs has been a slow process to date, although the efficacy of the drugs has been authenticated by several pharmaceutical bodies.

The compound Calanolide A was synthesized by Medichem chemists. The compound has demonstrated significant efficacy and a safe pharmacokinetic profile in HIV-negative healthy subjects. Calanolide B is still in preclinical development (Gupta & Gupta, 2020).

Phyllanthus Pulcher

This plant belongs to the Euphorbiaceae family and is native to Malaysia. The dried root powder of this plant has been commonly used for the treatment of gastric infections and ulcers (Salehi et al., 2018). However, due to the potency of the methanol extracts of this plant, it was tested for anti-HIV-1 reverse transcriptase (RT). This test was to be done through HIV-RT assay by inhibiting the HIV-1 RT enzyme based on their IC50 values. Azido-deoxythymidine triphosphate (AZT151TP) was used as a control in the assay. The results of this test indicated that the extracts of this plant contained anti-HIV properties that would be pharmaceutically useful in inhibiting HIV-1 virus from spreading to healthy T-cells (Cary & Peterlin, 2018).

Conclusions

In summary, it is clear that the use of plant-derived drugs is effective in the prevention of HIV and cancer. However, it is concerning that despite the early discovery of these compounds, their commercialization has been quite slow. This delay can be attributed to regulatory hurdles, such as the rigorous testing required to meet international safety standards, and financial barriers, including the high cost of clinical trials and limited funding for natural product research. Overcoming these challenges will be critical to accelerating the availability of plant-based medicines for widespread clinical use. Another growing concern is the potential extinction of plants in which anti-cancer and anti-HIV compounds have been found. The extinction of these plants would mean that the medicinal value of these discoveries would be lost, with possibly no chance of recovery, as was the case with the early discoveries of the anti-HIV plant Callophylum in the Borneo Islands, Malaysia. There is also a need to investigate how to accelerate the use of plant-derived anti-cancer and anti-HIV agents to intervene in cases where patients have adverse reactions or resistance to synthetic drugs and alternative treatment methods. Future research should focus on sustainable harvesting methods to conserve the biodiversity of medicinal plants, especially those at risk of extinction. In addition, overcoming bioavailability challenges, such as poor absorption and rapid metabolism of plant-derived compounds, will be critical. Advances in nanotechnology and drug delivery systems could play a key role in improving the therapeutic efficacy of these compounds.

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Review Article

The Role of the Tumor Microenvironment in Tumor Progression and Response to Therapy

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Abstract

The tumor microenvironment (TME) has emerged as a significant focus in cancer therapy due to its pivotal role in controlling tumor progression and shaping responses to conventional treatments. This review explores recent innovations in therapies targeting TME, including immunotherapies, antiangiogenic agents, and treatments aimed at cancer-associated fibroblasts and the extracellular matrix. These interventions, which are either approved for clinical use or undergoing clinical trials, underscore TME's influence on cancer treatment outcomes and patient survival. The identification of effective therapeutic strategies to target TME is imperative for mitigating immunosuppression, reactivating T cell functions, and enhancing immune system efficacy. Notwithstanding significant advancements, key gaps persist in comprehending the intricate interactions within TME and translating experimental findings into clinical success. Future research should prioritize elucidating these gaps to enhance therapeutic efficacy and patient outcomes.

Keywords: *TME, Tumor Incidence, Tumor Progression, Tumor Therapy.*

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Introduction

Cancer is among the top five leading causes of mortality worldwide, with a rapidly increasing prevalence. It is characterized by uncontrolled cell differentiation and proliferation, resulting in invasion, metastasis, and disrupted cellular homeostasis (Farc & Cristea, 2020; Q. Wang et al., 2023). The progression of tumors is significantly influenced by irregular immune responses and interactions between immune cells and cancer cells within the tumor microenvironment (TME). This dynamic interaction is a key driver of cancer growth and metastasis (Farc & Cristea, 2020; Q. Wang et al., 2023). TME encompasses various elements that sustain and promote tumor growth, including a diverse cellular composition and intercellular communication. This communication is mediated through mechanisms such as cytokines, chemokines, exosome, and desmosomes, which contribute to immune suppression and resistance to therapeutic interventions (Bożyk et al., 2022). However, contemporary therapeutic strategies targeting TME frequently encounter challenges, including off-target effects, limited clinical efficacy, and resistance mechanisms, underscoring the imperative for sustained research and the development of innovative approaches.

Tumor Microenvironment (TME)

The tumor microenvironment (TME) has been a subject of study since the late 19th century, beginning with Paget's "seed and soil" hypothesis in 1889, which expanded upon Virchow's 1863 concept linking inflammation to cancer (Bożyk et al., 2022; Jin & Jin, 2020; Ravensbergen et al., 2021). TME functions as an ecosystem comprising cancer cells in conjunction with components derived from both the tumor and the host, thereby playing a critical role in tumor growth, progression, and survival (Ravensbergen et al., 2021). TME essential elements include T and B lymphocytes, tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer (NK) cells, neutrophils, and myeloid-derived suppressor cells (MDSCs). Additional components consist of stromal cells like cancer-associated fibroblasts (CAFs), pericytes, and mesenchymal stromal cells, as well as the extracellular matrix (ECM), extracellular vesicles (EVs), and secreted growth factors. These elements collaborate to nourish tumors, provide oxygen, enable communication with cancer cells, suppress immune surveillance, and facilitate the delivery of therapeutic agents (Bejarano et al., 2021; Farc & Cristea, 2020; Tiwari et al., 2022; Q. Wang et al., 2023).

The dynamic interaction between the cellular and non-cellular components of TME contributes to tumor heterogeneity, clonal evolution, and resistance to multiple drugs (Bejarano et al., 2021; Farc & Cristea, 2020; Tiwari et al., 2022; Q. Wang et al., 2023). TME has been shown to comprise six distinct microenvironments, including the metabolic, immunological, mechanical, and innervated niches, each of which plays a role in tumor development (Farc & Cristea, 2020; Tiwari et al., 2022; Q. Wang et al., 2023).

Role of the Tumor Microenvironment (TME) in Cancer Initiation, Growth, and Progression

The tumor microenvironment (TME) is an intricate network integrated into the extracellular matrix (ECM). This network includes elements such as cytokines, growth factors, enzymes, proteoglycans, and glycoproteins (Bożyk et al., 2022; Ravensbergen et al., 2021).These elements are crucial in maintaining the structural integrity and equilibrium needed for tumor tissue proliferation and growth. A comprehensive understanding of their interactions, activation mechanisms, and functions is imperative for identifying and disrupting pathways that drive cancer progression (Bożyk et al., 2022; Ravensbergen et al., 2021). Hypoxia, defined as a state of insufficient oxygenation, is a pivotal factor influencing TME. It has been demonstrated that hypoxia promotes the expansion of regulatory lymphocytes, which suppress effector T cell activity, thereby creating favorable conditions for tumor development (Bożyk et al., 2022; Farc & Cristea, 2020; Razi et al., 2023; M. Wang et al., 2017; Q. Wang et al., 2023). Additionally, hypoxic environments stimulate neoplastic cells to release fibroblast growth factor (FGF), which attracts fibroblasts to the tumor site. These cancer-associated fibroblasts (CAFs) contribute to the formation of an abnormal extracellular matrix (ECM), the production of immunosuppressive cytokines, and the facilitation of angiogenesis, ultimately aiding tumor progression (Bożyk et al., 2022; Farc & Cristea, 2020; Razi et al., 2023; M. Wang et al., 2017; Q. Wang et al., 2023).

TME and Cancer Therapy

The recognition of the tumor microenvironment (TME) as a dynamic regulator of cancer progression and treatment responses has fueled the development of innovative therapies. Recent advances in this field have focused on targeting specific TME components or creating experimental models that replicate its complexity. These strategies encompass the activation of immune cells with antitumor properties and the suppression of pro-tumor immune cells within the TME, with the objective of disrupting its support for cancer growth (Aghanejad et al., 2022; Razi et al., 2023; Tsai et al., 2014; Q. Wang et al., 2023).

Targeting Monoclonal Antibodies and Combination Therapies

The interaction between programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1) plays a vital

role in maintaining immune system balance by suppressing T cell activation (Tsai et al., 2014; Q. Wang et al., 2023). Tumor cells exploit this pathway by overexpressing PD-L1, allowing them to evade immune detection and facilitate tumor growth. Immune checkpoint blockade (ICB) therapies, such as anti-PD-1/PD-L1 antibodies, function by preventing PD-1 from binding to PD-L1, reactivating T cells, and inhibiting tumor progression (Tsai et al., 2014; Q. Wang et al., 2023). Recent clinical trials have underscored the efficacy of ICB therapies. For instance, a meta-analysis of over 10,000 patients demonstrated a 25% increase in overall survival for advanced melanoma and non-small cell lung cancer (NSCLC) (Tsai et al., 2014; Q. Wang et al., 2023). However, heterogeneity in patient responses underscores the need for predictive biomarkers to optimize these therapies.

Radiotherapy and the Tumor Microenvironment (TME)

Radiotherapy (RT), a prevalent cancer treatment, exerts a substantial influence on the tumor microenvironment (TME) by modulating immune responses and modifying tumor-immune cell interactions. RT has been shown to enhance immune activation, trigger immunogenic cell death (ICD), and promote apoptosis in cancer cells. These effects are facilitated by pattern recognition receptors (PRRs) and damage-associated molecular patterns (DAMPs). Key DAMPs include secreted ATP, surface-exposed calreticulin (CRT), and high-mobility group protein B1 (HMGB1), which collectively contribute to immune stimulation (Monjazeb et al., 2020; Q. Wang et al., 2023).

Peptides and Macrocyclic Inhibitors

Immune checkpoint blockade (ICB) therapies have advanced significantly in recent years. Small molecule inhibitors have become increasingly popular due to their specificity, high binding affinity, low immunogenicity, favorable pharmacokinetics, cost-effectiveness, and ease of production. These inhibitors are widely used in research and clinical applications. Peptide-based vaccines, which mimic PD-1 epitopes, represent a promising avenue in cancer immunotherapy, offering targeted approaches to harness the immune system against tumors (Hao et al., 2020; Q. Wang et al., 2023).

Tumor-Associated Macrophages (TAMs)

Tumor-associated macrophages (TAMs) have been identified as pivotal contributors to cancer progression, exhibiting a multifaceted role in inflammation, tumor growth, metastasis, immune evasion, angiogenesis, and immunosuppression. In addition to these functions, TAMs have been shown to promote monocyte-derived macrophage (MDM) migration to residual tumors through increased colony-stimulating factor production, thereby facilitating cancer recurrence following conventional therapeutic interventions. Therapeutic approaches targeting TAMs include the following: blocking MDM recruitment and infiltration, preventing TAMs from differentiating into tumor-promoting phenotypes, and reducing proinflammatory cytokines and other signals within the TME (Hao et al., 2020; Q. Wang et al., 2023).

Chemokine (C-C Motif) Ligand 2/C-C Chemokine Receptor Type 2 (CCL2/CCR2)

CCL2-CCR2 axis plays a crucial role in cancer progression. By binding to its receptor CCR2, CCL2 drives cancer cell migration and recruits immunosuppressive cells to the tumor microenvironment (TME). This interaction supports tumor development by enhancing cell growth and proliferation. Over the past decades, CCL2-CCR2 signaling pathway has been extensively studied across various cancers. The development of novel therapeutic strategies that target this pathway has shown promise in enhancing cancer treatment outcomes (Hao et al., 2020; Y. Huang et al., 2017; Lu et al., 2020).

Cluster of Differentiation 47 (CD47), also Known as Integrin-Associated Protein (IAP)

CD47, a transmembrane protein belonging to the immunoglobulin superfamily, is widely expressed on cell membranes and plays a pivotal role in regulating cell migration, phagocytosis, and immune balance. Its interaction with SIRP, a receptor found on macrophages and dendritic cells, inhibits phagocytosis, allowing tumors to evade immune detection (Bejarano et al., 2021; L. Huang et al., 2014). CD47 is highly expressed in many cancers, making it a prominent target for immunotherapy. The inhibition of CD47 facilitates the innate immune system's ability to identify and eliminate cancer cells. Currently, several CD47 antagonists, including humanized 5F9, B6H12, and ZF1 antibodies, are undergoing phase I clinical trials, with varying outcomes concerning efficacy (Bejarano et al., 2021; L. Huang et al., 2014). Despite their apparent benefits, CD47-targeted therapies have given rise to concerns regarding off-tumor effects, including anemia and immunosuppression, which could potentially limit their clinical application.

Colony Stimulating Factor 1 Receptor (CSF1R)

These receptors play an instrumental role in regulating the survival, growth, and differentiation of mononuclear phagocytic cells. CSF-1/-1R axis exerts a substantial influence on tumor tissues, promoting the proliferation of tumor-associated macrophages (TAMs). This increase in TAMs contributes to tumor growth, angiogenesis, extracellular matrix degradation, invasion, and metastasis. The development of neutralizing antibodies and small-molecule inhibitors

that target CSF-1R has led to the potential for reducing TAM populations or reprogramming them toward tumor-suppressing phenotypes. Preclinical studies have demonstrated reduced metastasis and enhanced anticancer activity in breast cancer and other tumor models (Hao et al., 2020; Lu et al., 2020). However, CSF1R inhibitors have also demonstrated toxicity in preclinical studies, including liver enzyme elevations and hematological changes, which present barriers to clinical translation.

Myeloid-Derived Suppressor Cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that include pathologically activated neutrophils and monocytes. MDSCs are known to be highly immunosuppressive and are associated with poor cancer prognoses. These cells have been shown to promote tumor growth, inhibit T cell activation, and contribute to immune evasion in vitro and in vivo models. MDSCs are continually recruited to chronic inflammation sites, thereby sustaining their immunosuppressive effects despite their short lifespan. The development of effective therapeutic interventions to target MDSC activity may be a promising avenue for cancer treatment. Potential therapeutic strategies could involve the inhibition of MDSC activity at various levels, including the bone marrow, during tissue migration, or within the TME. Agents such as 5-fluorouracil, carboplatin, paclitaxel, and gemcitabine have been observed to reduce circulation of MDSCs, thereby enhancing antitumor immunity (Kramer & Abrams, 2020; Veglia et al., 2021). However, these agents are not selective and may also affect other rapidly proliferating cells, including beneficial T cells.

Fms-Like Tyrosine Kinase Receptor 3 (FLT3L)

FLT3 ligand (FLT3L) has been demonstrated to promote the differentiation of dendritic cells (DCs) from hematopoietic progenitors and enhance their functional activity (Bejarano et al., 2021; Cueto & Sancho, 2021; Favre-Felix et al., 2000). Administration of FLT3L in animal models has been shown to significantly increase DC populations in lymphoid and peripheral organs, enhance T cell priming, and inhibit tumor progression (Favre-Felix et al., 2000; Lee et al., 2019). FLT3L also supports the differentiation and growth of natural killer (NK) cells, contributing to antitumor responses (Lee et al., 2019). While FLT3L has demonstrated tumor regression in preclinical studies, combining FLT3L with other immunotherapeutic approaches may yield more effective outcomes by enhancing tumor antigen availability and boosting immune activation (Bejarano et al., 2021; Cueto & Sancho, 2021; Favre-Felix et al., 2000).

Cytotoxic T Lymphocyte Antigen-4 (CTLA4)

Immunotherapy targeting immune checkpoints has revolutionized the treatment and outcomes of solid tumors and hematological malignancies by enhancing long-term antitumor immune responses (De Silva et al., 2021; Seidel et al., 2018; Sobhani et al., 2021). CTLA-4 was the pioneering immune checkpoint receptor to be successfully targeted in clinical applications (Fleming et al., 2017). While CTLA-4 inhibitors, alone or in combination with anti-PD-1 antibodies, have shown significant therapeutic benefits, they are often associated with autoimmune-like adverse events (AEs) (Fleming et al., 2017; Sobhani et al., 2021). These AEs are often more severe in combination therapies, though they frequently correlate with improved clinical outcomes (De Silva et al., 2021; Seidel et al., 2018; Sobhani et al., 2021). Early detection and prompt treatment with immunosuppressive agents can effectively manage these AEs (Sobhani et al., 2021).

Lymphocyte Activation Gene-3 (LAG3)

In 1999, Frédéric Triebel and his research team identified lymphocyte activation gene-3 (LAG-3), an immune checkpoint receptor also known as CD223 or FDC protein (Triebel et al., 1999). LAG-3 gene encodes a 498-amino-acid transmembrane protein that belongs to the immunoglobulin superfamily and is located on chromosome 12 (Triebel et al., 1999). Elevated LAG-3 expression has been associated with unfavorable outcomes in various cancers, including renal clear cell carcinoma, non-small cell lung cancer, and hepatocellular carcinoma, while concurrently correlating with more favorable prognoses in melanoma and gastric cancer (Bejarano et al., 2021; Huo et al., 2022).

Within the context of the adaptive immune system, LAG-3 is expressed on both effector and regulatory T cells (Tregs), exerting its influence on the signaling pathways that mediate interactions between T cells and antigen-presenting cells (APCs). LAG-3 frequently coexists with PD-1 within the tumor microenvironment (TME), with both receptors functioning to suppress T cell activity through distinct mechanisms. Preclinical models of ovarian cancer, colon adenocarcinoma, and melanoma have demonstrated that the blockade of both LAG-3 and PD-1 has exhibited synergistic effects, enhancing antitumor responses (Bejarano et al., 2021; Huo et al., 2022).

Cluster of Differentiation 40 (CD40)

CD40, a transmembrane receptor, is expressed in a variety of cell types, including dendritic cells (DCs), myeloid cells, B cells, as well as endothelial, epithelial, fibroblastic, and certain malignant cells. Its primary ligand, CD40L, is expressed on activated T cells, B cells, and platelets. CD40/CD40L axis plays a critical

role in immune synapse formation, stimulating B cell activation, proliferation, and antigen presentation. A recent study by Djureinovic et al. (2021) and Salomon & Dahan (2022) demonstrated that agonistic anti-CD40 antibodies enhance dendritic cell (DC) maturation, antigen presentation, and the proliferation of tumor antigen-specific cytotoxic T cells, thereby enabling the immune system to eradicate tumors.

T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT)

TIGIT, a co-inhibitory receptor belonging to the same family as PD-1, CTLA-4, and LAG-3, regulates T cell responses. Identified through bioinformatics approximately 15 years ago, TIGIT is expressed on memory T cells, natural killer (NK) cells, and other immune cells. It is overexpressed in the TME of various cancers, including lungs, kidneys, liver, glioma, and melanoma. Its high expression has been associated with unfavorable prognoses in multiple cancers, including renal cell carcinoma and low-grade gliomas. Inhibiting TIGIT, particularly in combination with PD-1/PD-L1 inhibitors, has shown anticancer effects in preclinical studies (Chauvin & Zarour, 2020; Chu et al., 2023; Rousseau et al., 2023).

Conclusions

The field of research concerning the tumor microenvironment (TME) is undergoing rapid evolution, presenting both challenges and opportunities. A more profound comprehension of the TME's function in cancer immune processes and progression has the potential to result in groundbreaking advancements in tumor-immune precision medicine. TME exerts a pivotal influence on treatment outcomes and survival rates for cancer patients. The identification of targeted strategies to overcome immunosuppression, restore T cell functionality, and enhance immune responses is imperative for the enhancement of therapeutic outcomes. The therapeutic strategies reviewed in this manuscript illustrate significant translational potential, particularly in enhancing immune system function and disrupting tumor-supportive mechanisms within the TME. Future efforts should focus on refining these therapies to minimize adverse effects, improve specificity, and integrate them with existing treatment modalities. By addressing these challenges, these innovations could pave the way for more personalized and effective cancer therapies.

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Research Article

Exploring Knowledge and Awareness of Genetic Testing for Breast Cancer Risk in Iraqi Women

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Abstract

Background: *Genetic testing plays a crucial role in identifying individuals at risk for hereditary breast cancer. However, substantial gaps in understanding genetic risk factors, including BRCA1/BRCA2 mutations, and key barriers such as high costs, limited access, and cultural stigma remain significant challenges in Iraq. These barriers hinder the adoption of genetic testing, particularly in low-resource settings. This study aims to evaluate the knowledge and awareness of genetic testing among Iraqi women in Baghdad, highlighting key barriers and their implications for healthcare delivery.*

Methods: *A cross-sectional study was conducted among 520 Iraqi women in Baghdad using a structured self-administered questionnaire. The questionnaire assessed knowledge of genetic risk factors, awareness of genetic testing services, and perceived barriers to testing. The collected data were then subjected to analysis using descriptive statistics and chi-square tests to ascertain the associations between socio-demographic factors and the levels of knowledge and awareness. A p-Value less than 0.05 was considered statistically significant.*

Results: *The study revealed moderate knowledge of genetic testing, with 280 respondents recognizing its role in identifying individuals at risk and 300 acknowledging the importance of genetic counseling. However, the study also revealed a lack of awareness regarding the significance of specific genetic mutations, such as BRCA1 and BRCA2, with only 190 respondents reporting familiarity with these mutations. Furthermore, the study noted a general lack of awareness about available genetic testing services, with only 260 participants reporting knowledge of their availability and 200 aware of the availability of genetic counseling services. The analysis identified several key barriers to genetic testing and counseling, including perceived financial constraints (320 respondents), limited access to facilities (300 respondents), and societal stigma (240 respondents). Significant associations were identified between higher education level and urban residency, on the one hand, and better knowledge and awareness, on the other.*

Conclusion: *The findings underscore the necessity for targeted educational programs, improved access to testing services, and culturally sensitive interventions to enhance the uptake of genetic testing in Iraq, ultimately contributing to early detection and prevention of breast cancer.*

Keywords: *Genetic Testing, Breast Cancer, BRCA1, BRCA2, Knowledge, Awareness, Iraq, Public Health.*

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Introduction

Breast cancer is the most common malignancy among women worldwide and represents a critical challenge to healthcare systems worldwide. In 2020 alone, breast cancer will account for 2.3 million new cases and 685,000 deaths, underscoring its significant public health burden (Singh et al., 2024; Sung et al., 2021). Early detection through advanced tools, including genetic testing, has been instrumental in reducing mortality and improving long-term outcomes. Genetic testing for hereditary breast cancer risk factors, particularly BRCA1 and BRCA2 gene mutations, enables early identification of high-risk individuals, allowing for personalized prevention and treatment strategies (Rebbeck et al., 2015). Women with BRCA mutations have up to a 72% lifetime risk of developing breast cancer, highlighting the importance of increasing awareness and improving access to genetic testing (Kuchenbaecker et al., 2017).

Despite the established benefits, uptake of genetic testing remains limited in low- and middle-income countries, including Iraq, due to lack of awareness, cultural stigma, and limited access to healthcare resources (Alwan, 2010). In Iraq, breast cancer is the most commonly diagnosed cancer among women, accounting for 19.5% of all cancers (Al Alwan, 2022). However, many cases are diagnosed at advanced stages when treatment options are limited and prognosis is poor. This late diagnosis is often attributed to a lack of knowledge about breast cancer and its prevention, including genetic testing. Filling this knowledge gap is critical to improving early detection and reducing mortality in this population.

Awareness and knowledge of genetic testing are strongly influenced by sociodemographic factors such as education, age, and urban versus rural residence. Previous studies have highlighted the association between higher levels of education and increased awareness of breast cancer prevention strategies, including genetic testing (Hasan et al., 2015). Urban women are more likely to have access to healthcare resources and educational campaigns, while rural populations face significant barriers, including inadequate healthcare infrastructure and cultural taboos (McCall-Hosenfeld & Weisman, 2011). In Iraq, where disparities in access to health care and education are pronounced, understanding these sociodemographic influences is critical to designing effective interventions.

Cultural beliefs and misconceptions also play an important role in shaping attitudes toward genetic testing. Fear of stigma, concerns about the cost of testing, and anxiety about the implications of genetic results are commonly reported barriers (Bruno et al., 2004). In addition, the lack of integration of genetic counseling services into primary health care further limits the accessibility of genetic testing for high-risk populations (Jones et al., 2021). Overcoming these barriers will require targeted awareness campaigns and health system reforms that prioritize genetic counseling and testing as integral components of breast cancer prevention.

While previous research in Iraq has predominantly focused on breast cancer awareness, few studies have examined the specific knowledge and barriers associated with genetic testing for breast cancer risk. Existing studies, such as those by Hasan et al. (2015) and Alwan (2010), emphasize general cancer awareness but neglect the role of genetic risk factors such as BRCA1 and BRCA2 mutations. This study uniquely contributes to the literature by addressing this gap and identifying sociodemographic predictors and barriers, including cost, accessibility, and cultural stigma, which are critical for tailoring public health strategies in the Iraqi context. By focusing specifically on knowledge and awareness of genetic testing, this research provides actionable insights for integrating genetic services into local health systems.

This study aims to assess knowledge and awareness of genetic testing for breast cancer risk among Iraqi women in Baghdad. By identifying key socio-demographic predictors and barriers to awareness, this research seeks to provide evidence-based recommendations for improving public health strategies. The findings will contribute to a better understanding of the challenges and opportunities for promoting genetic testing in Iraq, ultimately aiding in the early detection and prevention of breast cancer.

Methods

Study Design

This cross-sectional study was conducted to assess knowledge and awareness of genetic testing available for breast cancer risk detection among Iraqi women in Baghdad. A structured self-administered questionnaire was used, adapted from validated tools developed to assess knowledge and awareness of genetic testing in breast cancer prevention. Specifically, the questionnaire was adapted from studies by Jones et al. (2021) and Vadaparampil et al. (2010), with modifications to ensure cultural and contextual relevance to the Iraqi population (Jones et al., 2021; Vadaparampil et al., 2010).

Questionnaire Development

The questionnaire consisted of three sections and was structured to comprehensively assess knowledge and awareness. Section A collected sociodemographic information, including age, marital status, education level, and location. Section B focused on knowledge of genetic testing, with items addressing the role of BRCA1 and BRCA2 mutations, the purpose of genetic

testing, and the benefits of genetic counseling. Section C assessed awareness of genetic testing services, including availability, accessibility, and perceived barriers such as cost, stigma, and fear of test results.

The adaptation process ensured that the questionnaire was consistent with the objectives of the study and relevant to the Iraqi context. Items were translated into Arabic and pre-tested on a sample of 50 Iraqi women to assess clarity, comprehension, and cultural appropriateness. Feedback from the pretest informed adjustments to the wording and structure of the questionnaire.

To assess the reliability of the adapted questionnaire, a pilot test was conducted with 50 participants prior to the main study. Cronbach's alpha values were calculated for each section, yielding values of 0.82 for knowledge items and 0.78 for awareness items, indicating acceptable internal consistency. Content validity was assessed by a panel of three experts in oncology and public health who reviewed the items for clarity, cultural appropriateness, and relevance to the Iraqi context. Based on their feedback, minor modifications were made to improve item clarity and cultural sensitivity.

Sampling Method

Participants were recruited using convenience sampling to include adult women aged 18 years and older who had lived in Baghdad for at least five years. Women with a professional or academic background in genetics or oncology were excluded to minimize bias in the knowledge assessment. A total of 520 participants were recruited, equally divided between health professionals, such as pharmacists and physicians, and women from non-health fields. This stratification allowed the study to capture different perspectives on knowledge and awareness. A convenience sampling approach was used to recruit participants from urban health facilities in Baghdad. While this method facilitated accessibility and participant recruitment, it may limit the generalizability of the findings to the broader population, particularly women in rural areas or those with limited access to health services. To minimize bias, efforts were made to include a diverse sample of participants from different socio-demographic groups.

Data Collection

Data was collected over three months, from June to August 2023, at various urban and semi-urban locations in Baghdad, including universities, health centers, and community events. Research assistants were trained to provide participants with detailed explanations of the study objectives and instructions for completing the survey. Participants completed the questionnaire independently, with assistance available upon request for questions or clarification.

Data Analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) software version 29. Descriptive statistics, such as frequencies and percentages, were used to summarize demographic characteristics, knowledge levels, and awareness scores. Inferential statistics, including the chi-squared test, were used to determine associations between sociodemographic variables and participants' knowledge and awareness of genetic testing. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

Ethical approval for the study was obtained from the Al-Rafidain University College Research Ethics Committee (REC: 46-2023). All participants gave written informed consent after being informed of the study objectives, procedures, and confidentiality measures. Participation was voluntary, and participants were assured of their right to withdraw at any time without repercussions.

Results

Table 1 summarizes the sociodemographic characteristics of the 520 participants in this study. The largest age group consisted of participants aged 31-50 years (44.2%), followed by those aged 18-30 years (40.4%). Only a small proportion of participants were 51 years or older (15.3%). Regarding educational attainment, the majority had at least a bachelor's degree (44.2%), 11.5% had a master's degree, and 1.9% had a doctorate. Secondary school graduates accounted for 32.7% of the sample, while 9.6% had completed only primary school. Half of the participants (50.0%) were single, 46.2% were married, and a minority were divorced or widowed (3.8%). The majority of the sample was urban (71.2%), compared to 28.8% from rural areas. These sociodemographic patterns provide valuable context for interpreting the knowledge and awareness levels of the study population.

Table 1. Socio-Demographic Characteristics of Respondents (N=520)

Variable	Frequency (n)	Percentage (%)
Age Group (Years)		
18–30	210	40.4
31–50	230	44.2
51–64	60	11.5
≥ 65	20	3.8

Variable	Frequency (n)	Percentage (%)
Education Level		
Primary School	50	9.6
Secondary School	170	32.7
Bachelor's Degree	230	44.2
Master's Degree	60	11.5
Doctorate Degree	10	1.9
Marital Status		
Single	260	50.0
Married	240	46.2
Divorced/Widowed	20	3.8
Place of Residence		
Urban Area	370	71.2
Rural Area	150	28.8

Knowledge of Genetic Testing for Breast Cancer Risk

Table 2 shows the knowledge of genetic testing for breast cancer risk among the 520 respondents. The highest correct response rate (57.7%) was observed for the item "Genetic counseling is important before and after genetic testing," indicating a relatively good understanding of the importance of genetic counseling. More than half of the participants (53.8%) correctly recognized that genetic testing helps to identify individuals at risk, while 51.9% correctly recognized the importance of family history in genetic testing. In contrast, knowledge of BRCA1 and BRCA2 mutations was lower, with only 36.5% of participants aware of their role in increasing breast cancer risk. In addition, 46.2% correctly stated that genetic testing is not appropriate for all women, and 40.4% understood that results could influence treatment options. These findings highlight significant gaps in knowledge about specific aspects of genetic testing, particularly related to BRCA mutations and treatment implications.

Table 2. Knowledge of Genetic Testing for Breast Cancer Risk (N=520)

Knowledge Items	Correct Responses (n)	Percentage (%)
Genetic testing can help identify individuals at risk of breast cancer.	280	53.8
BRCA1 and BRCA2 mutations increase breast cancer risk.	190	36.5
Genetic testing can guide preventive measures, such as surgery.	230	44.2
Genetic testing requires a family history of breast cancer.	270	51.9
Genetic counseling is important before and after genetic testing.	300	57.7
Genetic testing is not suitable for all women.	240	46.2
Results of genetic testing can influence treatment options.	210	40.4

Awareness of Genetic Testing Services and Perceived Barriers

Table 3 shows the level of awareness and perceived barriers to genetic testing services among the 520 respondents. Half of the participants (50.0%) were aware of the availability of genetic testing for breast cancer risk, while awareness of genetic counseling services was lower at 38.5%. The most commonly reported barrier was the perception that genetic testing is expensive, with 61.5% of respondents expressing this concern. In addition, 57.7% of participants perceived limited access to testing facilities as a barrier, and 53.8% expressed concern about receiving positive test results. Nearly half of respondents (46.2%) felt there was a stigma associated with genetic testing. These findings underscore the need to address cost, accessibility and societal perceptions to improve uptake of genetic testing services in this population.

Table 3. Awareness of Genetic Testing Services and Perceived Barriers (N=520)

Awareness and Barrier Items	Frequency (n)	Percentage (%)
Aware of the availability of genetic testing for breast cancer risk.	260	50.0
Aware of genetic counseling services.	200	38.5
Believing genetic testing is expensive.	320	61.5
Feels stigma are associated with undergoing genetic testing.	240	46.2

Awareness and Barrier Items	Frequency (n)	Percentage (%)
Concerns about receiving positive results from testing.	280	53.8
Perceived lack of access to testing facilities.	300	57.7

Association Between Socio-Demographic Characteristics and Knowledge of Genetic Testing

Table 4 shows the association between sociodemographic characteristics and knowledge of genetic testing for breast cancer risk among respondents. Level of education was significantly associated with knowledge (χ^2 = 12.87, p = 0.001), indicating that participants with higher levels of education were more likely to have better knowledge. Place of residence was also a significant factor (χ^2 = 9.65, p = 0.004), with urban residents demonstrating greater knowledge than those from rural areas. No significant associations were found between knowledge and age (χ^2 = 3.24, p = 0.072) or marital status (χ^2 = 1.98, p = 0.086). These findings highlight the importance of educational and geographic differences in shaping awareness and knowledge of genetic testing in this population.

Table 4: Association Between Socio-Demographic Characteristics and Knowledge of Genetic Testing (N=520)

Variable	χ^2 Value	p-Value
Age	3.24	0.072
Education Level	12.87	0.001**
Marital Status	1.98	0.086
Place of Residence	9.65	0.004**

: **p < 0.05 is considered statistically significant.

Association Between Socio-Demographic Characteristics and Awareness of Genetic Testing

Table 5 illustrates the relationship between socio-demographic characteristics and awareness of genetic testing services among respondents. Level of education was significantly associated with awareness (χ^2 = 14.21, p = 0.001), with higher levels of education correlating with greater awareness. Place of residence also showed a significant association (χ^2 = 11.34, p = 0.003), as participants living in urban areas were more likely to be aware of genetic testing services compared to their rural counterparts. No significant associations were found for age (χ^2 = 2.94, p = 0.088) or marital status (χ^2 = 1.45, p = 0.112). These findings highlight the critical role of education and geographic location in determining awareness levels and underscore the need for targeted outreach efforts in rural and less educated populations.

Table 5: Association Between Socio-Demographic Characteristics and Awareness of Genetic Testing (N=520)

Variable	χ^2 Value	p-Value
Age	2.94	0.088
Education Level	14.21	0.001**
Marital Status	1.45	0.112
Place of Residence	11.34	0.003**

: **p < 0.05 is considered statistically significant.

Discussion

This study assessed knowledge and awareness of genetic testing for breast cancer risk among Iraqi women in Baghdad. The results revealed significant gaps in understanding and highlighted important socio-demographic disparities. These findings provide a basis for improving public health initiatives aimed at increasing genetic literacy and improving access to genetic services.

Knowledge of Genetic Testing

The study found moderate levels of knowledge among participants, with 280 respondents recognizing the role of genetic testing in identifying individuals at risk and 300 recognizing the importance of genetic counseling. However, only 190 participants were aware of the critical role of BRCA1 and BRCA2 mutations. This limited awareness of genetic mutations is concerning because it underscores a significant gap in the understanding of important genetic factors that have been extensively linked to cancer risk. Kuchenbaecker et al. (2017) demonstrated that women who carry BRCA mutations face a substantially increased risk of breast and ovarian cancer, with lifetime risks exceeding 50% for some individuals (Kuchenbaecker et al., 2017). Lack of awareness of these mutations may hinder proactive risk management and early intervention, which are essential to reducing morbidity and mortality associated with hereditary cancers. This is consistent with Alwan (2010), who found that underserved populations in particular often lack access to accurate information and genetic testing resources, exacerbating disparities in preventive health measures (Alwan, 2010).

In addition, the study revealed significant misconceptions about the practical applications of genetic testing. For example, only 210 participants recognized that genetic test results could guide treatment decisions, revealing a significant gap in understanding of the clinical utility of genetic testing. This deficit reflects a broader trend identified by Bruno

et al. (2004), who reported that while the general public may have heard of genetic testing, specific knowledge of how such testing can impact treatment planning, such as selecting targeted therapies or determining the appropriateness of preventive surgery, remains limited (Bruno et al., 2004). These gaps are particularly troubling given that genetic testing can provide critical information for personalized medicine approaches, including identifying patients who would benefit from targeted therapies such as PARP inhibitors for BRCA-mutated cancers (Grech et al., 20-22; McCuaig et al., 2018).

These findings highlight the urgent need for comprehensive educational campaigns to improve public understanding of genetic testing and counseling (Chappuis et al., 2000; Metcalf et al., 2010). Such initiatives should address both the general concept of genetic testing and its specific applications in clinical practice. Programs must simplify complex genetic information to ensure accessibility and focus on practical benefits, such as personalized treatment options and prevention strategies (JOKIĆ-BEGIĆ & ARAMBAŠIĆ, 2010). In addition, integrating these educational efforts into broader public health campaigns could increase their reach, particularly in underserved communities where misinformation and limited access to resources are prevalent. Increasing public knowledge in this area could ultimately improve health outcomes by promoting early detection, timely intervention, and informed decision-making regarding genetic testing and counseling (Radford et al., 20-21).

Awareness of Genetic Testing Services and Barriers

Awareness of genetic testing services was low, with only 260 participants aware of their availability and even fewer (200 respondents) aware of genetic counseling. This finding is consistent with Vadaparampil et al. (2010), who found significant gaps in awareness of genetic testing and counseling services among at-risk populations. Similarly, several studies have found limited awareness of breast cancer prevention strategies among women in Baghdad, which mirrors the challenges faced in this study (Hasan et al., 2015; Hassan et al., 2022).

Barriers to genetic testing were prominent, with cost (320 respondents), limited access to facilities (300 respondents), and stigma (240 respondents) frequently cited. These challenges echo findings from similar contexts. In Iraq, Alwan (2010) reported that financial constraints and limited health infrastructure often impede access to advanced diagnostic tools, including genetic testing (Alwan, 2010). The cultural stigma associated with genetic testing, as seen in this study, reflects societal misconceptions and fears that have also been reported in Jordan and other Middle Eastern countries (Hasan et al., 2015).

Socio-Demographic Predictors

Education level and urban residence emerged as significant predictors of both knowledge and awareness. Participants with higher education demonstrated greater understanding of genetic testing, consistent with findings from a previous literature review that highlighted the role of education in improving health literacy and awareness of cancer prevention (McCall-Hosenfeld & Weisman, 2011). Urban residence was also associated with higher levels of knowledge and awareness, reflecting disparities in health care access between urban and rural populations. Hasan et al. (2015) similarly found that urban women in Baghdad had better access to health resources and information than their rural counterparts (Hasan et al., 2015).

Implications for Public Health

This study highlights the need for comprehensive public health strategies to address the gaps in knowledge and awareness of genetic testing for breast cancer. Educational campaigns should focus on increasing understanding of genetic risk factors, the importance of genetic counseling, and the availability of testing services. Following the successful approaches outlined by Bruno et al. (2004), integrating genetic education into routine health care services can improve awareness and acceptance (Bruno et al., 2004). In addition, reducing financial and logistical barriers by subsidizing costs and expanding access to rural areas could improve uptake (Emmet et al., 2018; Fogleman et al., 2019; Li et al., 2017). Culturally tailored interventions are also essential to address stigma and normalize genetic testing in Iraq.

Limitations and Future Directions

This study has several limitations that should be acknowledged. First, the use of convenience sampling may limit the generalizability of the findings to the broader population of Iraqi women. Participants recruited from urban health facilities may have had better access to information and resources than those in rural areas, potentially biasing the results. Second, the reliance on self-reported data introduces the possibility of recall and social desirability bias, where participants may have over- or under-reported knowledge or awareness. These biases may have affected the accuracy of the results. Future research should use representative sampling methods and explore additional regions to provide a more comprehensive understanding of genetic testing knowledge and barriers in Iraq.

Conclusion

This study highlights significant gaps in knowledge and awareness of genetic testing for breast cancer risk among Iraqi women in Baghdad. Addressing these disparities through targeted educational programs, improved access to genetic services, and culturally

sensitive strategies is critical to empowering women and improving early detection efforts in Iraq.

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Review Article

Assessing Chemotherapy-Induced Nausea and Vomiting in Breast Cancer Patients in Malaysia: Insights into Quality of Life and Genetic Influences

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Abstract

Background: *Malaysia faces a persistent public health challenge in the form of breast cancer, which affects approximately one in twenty women and accounts for a significant proportion of cancer-related mortality across diverse ethnic groups and age demographics. Despite the advancements in cancer therapeutics, the side effects of chemotherapy, particularly nausea and vomiting, continue to profoundly impact the quality of life of breast cancer patients.*

Objective: *The objective of this scoping review is to explore the prevalence, management practices, and factors contributing to chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients in Malaysia, with a focus on its implications for patient care and treatment outcomes.*

Methodology: *A systematic search of PubMed, Scopus, and local Malaysian journals was conducted to identify relevant studies. The articles identified were then screened and selected based on predefined inclusion criteria. Key themes related to CINV prevalence, management strategies, and patient outcomes were extracted and synthesized.*

Findings: *The review's findings underscore the prominence of nausea and vomiting as major side effects of breast cancer chemotherapy, leading to complications such as poor treatment adherence and suboptimal response rates. The analysis indicates that current management practices within Malaysia's healthcare system are inadequate in alleviating the severity of CINV or enhancing patients' quality of life. Furthermore, the multiethnic composition of the Malaysian population introduces genetic variations that influence drug metabolism, resulting in disparities in treatment efficacy and tolerability.*

Conclusion: *The findings underscore the critical impact of CINV on the quality of life of breast cancer patients, highlighting the necessity for a re-evaluation of existing treatment guidelines and the development of customized strategies tailored to the Malaysian population. Enhancing CINV prevention and management practices has the potential to markedly improve patient health outcomes and treatment success.*

Keywords: *Breast Cancer, Malaysia, Chemotherapy-Induced Nausea and Vomiting, Quality of Life, Genetic Variations.*

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Introduction

Among women, breast cancer accounts for 14% of all cancer-related fatalities and 23% of all new cancer cases each year, making it a significant burden on healthcare systems worldwide (Ibrahim et al., 2012; Jemal et al., 2011). This disease disproportionately affects developing nations, accounting for over 60% of fatalities and 50% of new cases. A global perspective reveals that the incidence rate is highest in North America, Northern Europe, Northern Africa, and Australia and New Zealand; it is intermediate in South America and Northern Africa; and it is relatively low in Asia, Central Africa, and Southern Africa. The disparities in breast cancer incidence can be attributed to various factors, including reproductive and hormonal influences, as well as the accessibility of screening programs (Dahlui et al., 2011; Ibrahim et al., 2012; Jemal et al., 2011; World Health Organization, 2008).

Despite the ongoing rise in incidence, there has been a decline in breast cancer fatality rates. From 1971 to 2007, the number of individuals who have survived breast cancer increased fourfold, from three million to over twelve million (Aapro, 2004). Despite the strides made in treatment outcomes, a significant proportion of patients undergoing chemotherapy continue to encounter adverse effects, including nausea, vomiting, diarrhea, anemia, leucopenia, neutropenia, and thrombocytopenia. Chemotherapy-induced nausea and vomiting, in particular, persist as debilitating side effects despite efforts to prevent and alleviate them (Aapro, 2004).

These symptoms can be particularly challenging to manage, often resulting in significant discomfort and impaired quality of life for patients undergoing cancer treatment. The inadequate management of these symptoms can lead to a reduction in patients' appetite and thirst, which, in turn, can compromise treatment efficacy, increase the risk of mortality and morbidity, and escalate healthcare expenditures (Aapro, 2004). A novel approach to managing these symptoms involves the combination of corticosteroids and 5-HT3 (serotonin3)-receptor antagonists, with the objective of enhancing therapeutic efficacy.

In Malaysia, these challenges are exacerbated by the unique healthcare and cultural context. The country's multiethnic composition, encompassing Malay, Chinese, Indian, and indigenous communities, introduces variations in genetic predispositions, treatment responses, and healthcare access. The disparities in healthcare access between rural and urban areas, compounded by disparities in health literacy, further complicate the management of CINV. The limited availability of specialized cancer care and antiemetic medications, in conjunction with cultural perceptions regarding cancer and its treatment, can also influence patients' decisions regarding treatment-seeking and adherence.

Despite the proliferation of research on breast cancer and its treatment, a comprehensive review study focusing on Malaysia has not been conducted to date. The primary objective of this article is to provide an overview of clinical studies investigating the risk factors for nausea and vomiting in breast cancer patients in Malaysia. We further aim to explore the approaches employed in preventing and treating these significant side effects through personalized therapy and effective treatment guidelines.

Methods

This scoping review was conducted to synthesize evidence on chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients in Malaysia, with a particular focus on genetic influences, treatment efficacy, and quality of life. The review followed a systematic approach to ensure the inclusion of relevant studies and comprehensive coverage of the topic. The synthesis of findings was methodically conducted on the basis of nine studies that met predefined inclusion criteria. These criteria included studies conducted in Malaysia, with a primary focus on breast cancer-related CINV, and addressing genetic influences, treatment efficacy, or quality of life. Studies conducted outside of Malaysia or lacking specific relevance to CINV in breast cancer patients were excluded from the review.

Search Strategy

A comprehensive search of peer-reviewed articles was conducted across databases, including PubMed, Scopus, and Google Scholar. A combination of keywords, including "chemotherapy-induced nausea and vomiting," "breast cancer," "Malaysia," and "genetic polymorphism," was employed to identify relevant studies. To ensure comprehensive coverage, manual searches of references from selected articles were also performed.

Data Extraction

The data extracted from the selected studies included the study design, sample characteristics, focus on genetic influences, quality of life measures, and antiemetic treatment protocols. A particular emphasis was placed on the identification of gaps in current practices and the highlighting of genetic variations across Malaysia's multiethnic population.

Analysis

The findings from the included studies were summarized and synthesized narratively to provide insights into the prevalence, management, and impact of CINV on breast cancer patients' quality of life. The

analysis placed particular emphasis on the role of genetic factors in determining the efficacy of antiemetic treatments and the variability in treatment outcomes.

Findings

Despite the implementation of preventive healthcare initiatives, the incidence of breast cancer continues to increase in Asia. A notable variation in breast cancer incidence rates is observed among Asian countries. For instance, the rate in Singapore is 54 per 100,000, whereas in Iran it is 21.4, in Turkey it is 24.1, in Malaysia it is 34.84, and in Jordan it is 48 (Ahmadian & Samah, 2013). A comprehensive review of the literature reveals that Korea had the highest breast cancer death rate during the mid-1980s to the mid-1990s, with China and Japan following closely behind (Ahmadian & Samah, 2013; Bloechl-Daum et al., 2006; Bray et al., 2004; Harirchi et al., 2004; Hisham & Yip, 2004; Petro-Nustus & Mikhail, 2002; Secginli & Nahcivan, 2006). A comprehensive assessment indicates that de novo metastatic cancer is two to three times more prevalent in Asian women (10-25% vs. 2% to 1% in European and American women). Furthermore, metastases in Asian women are frequently more substantial in size and encompass multiple sites (Miao et al., 2014).

A significant challenge in addressing this issue is the limited accessibility to mammography screenings in many Asian countries. Recent data indicates that 12% of South Asian women, 25% of Turkish women, and less than 10% of women in China, Iran, and the UAE undergo mammography (Ahmadian & Samah, 2013; Schwartz et al., 2008).

Breast Cancer in Malaysia

In Malaysia, breast cancer is the most prevalent form of cancer among women, accounting for 26.5% of all malignancies in 2008. The nation's population, estimated at 28.3 million, is a heterogeneous blend of Malay, Chinese, and Indian ethnic groups. The following cancers are in order of prevalence: cervical (12.6%), colorectal (9.9%), lung (5.8%), and ovarian (5.4%). The breast cancer incidence rate in Malaysia is higher than in neighboring countries like Thailand and Indonesia (Mallick & Cheen, 2013). A study by Yusuf et al. (2013) revealed that 32.1% of all diagnosed cancers in Malaysian females are breast cancers, with 58.2% of these cases detected in their early stages and 42.0% in their later stages (Yusuf et al., 2013; Zainal Ariffin & Nor Saleha, 2011). This type of cancer accounts for approximately 11% of all recorded fatalities among Malaysian women and is the primary cause of cancer-related mortality (Chin Chye et al., 2008; Hadi et al., 2010; Yusuf et al., 2013). Among Malaysia's three primary ethnic groups, the Chinese had the highest incidence rate of 38.1 per 100,000, followed by the Indians at 33.7 per 100,000, and the Malays at 25.4 per 100,000 (Chin Chye et al., 2008; Hassan & Yusoff, 2011; Yusuf et al., 2013; Zainal Ariffin & Nor Saleha, 2011). The varying rates of occurrence among ethnic groups may be explained by differences in lifestyle, nutrition, genetics, and reproductive factors such as sexual behavior, age at which a woman becomes pregnant, and breastfeeding habits (Hadi et al., 2010). The Malay population exhibits the lowest incidence of the disease, yet they also demonstrate the lowest survival rate, as the disease often manifests at a later stage and with larger tumors (Ibrahim et al., 2012; Mujar et al., 2013; Taib et al., 2011; Yip et al., 2006; Yusuf et al., 2013).

Chemotherapy-Induced Nausea and Vomiting (CINV)

Chemotherapy presents considerable challenges for cancer patients due to its associated debilitating side effects, including nausea and vomiting, which can occasionally exceed the impact of the underlying disease (Mustian et al., 2011). CINV stands as a prime example of the deleterious side effects that can profoundly impact the quality of life (QOL) of breast cancer patients. It can have detrimental effects on patients' mental and physical well-being. The propensity for CINV varies according to the specific chemotherapy regimen employed, with certain regimens demonstrating a higher risk than others (Grunberg et al., 2013). The emetogenic risk associated with the majority of chemotherapeutic agents employed in the treatment of breast cancer ranges from low to moderate. Despite the utilization of various antiemetic medications, the prevalence of CINV among patients remains persistently high, ranging from 40% to 75% (Booth et al., 2007; Choi et al., 2005; Hesketh, 2005; Kottschade et al., 2016; O'Shaughnessy, 2003). The most efficacious antiemetic medications are 5-HT3 and NK-1 receptor antagonists (Grunberg et al., 2013). A plethora of studies have investigated nausea and vomiting induced by cancer therapy; however, few prospective observational studies have exclusively focused on breast cancer treatment and the associated risk factors for these side effects in these patients (Hesketh, 2005). The majority of research in this field has primarily examined the effects of CINV on patients' QOL, with limited studies specifically addressing solid cancer patients (Booth et al., 2007; Choi et al., 2005; Hesketh, 2005; O'Shaughnessy, 2003; Rhodes & McDaniel, 2001).

This review encompasses a total of nine studies (four cross-sectional, three observational, one descriptive study, and one case report) that investigate the occurrence of Chemotherapy-Induced Nausea and Vomiting (CINV) among breast cancer patients in Malaysia.

To evaluate the treatment of acute CINV, Dewan et al. (2010) enrolled 35 breast cancer patients based in

Kuala Lumpur in a prospective research study. Participants were interviewed within five days following their most recent chemotherapy treatment for breast cancer. The majority of the participants were female (71.4%) and Malay (63%). The ages of the participants ranged from 51 to 60 years (34%). The administration of granisetron and dexamethasone, in conjunction, over a five-day period, resulted in a 50% reduction in nausea and an 87.5% reduction in vomiting, both in the acute and delayed stages. Furthermore, at the conclusion of chemotherapy, patients who received a five-day combination of dexamethasone and metoclopramide exhibited an 18.5% reduction in emesis control compared to those who received the alternative combination. Furthermore, the addition of granisetron to dexamethasone post-chemotherapy resulted in complete control of nausea and vomiting. The study by Dewan et al. (2010) found a significant correlation between the emetogenic potential of the chemotherapy regimen and the frequency of emesis.

A case report by Gupta et al. (2021) documented the treatment of a Malay woman in her mid-40s diagnosed with cancer of the right breast, who received 110 g of docetaxel and cisplatin. The patient received dexamethasone with granisetron 30 minutes prior to chemotherapy, and no instances of CINV were observed (Gupta et al., 2021).

In 2010, Hassan & Yusoff conducted a longitudinal observational prospective study with 158 breast cancer patients who had three to five days of chemotherapy. The objective of the study was to ascertain the impact of acute chemotherapy-induced nausea and vomiting (CINV) on patients' quality of life and their perceptions of antiemetic protocols. The results of the study indicated that, in comparison with acute CINV and vomiting, delayed CINV exerted a more substantial impact on patients' quality of life (QOL) and control. The authors further noted that patients' perspectives and responses to antiemetic medications appeared to be significantly influenced by genetic variations (Hassan & Yusoff, 2010).

In 2011, researchers in Malaysia embarked on an investigation to ascertain the impact of genetic polymorphism on the antiemetic efficacy of granisetron across the three most prevalent ethnic groups in the nation: Malay, Chinese, and Indian. The study population comprised 158 breast cancer patients, with the majority (93%) undergoing treatment with the FEC (fluorouracil, epirubicin, cyclophosphamide) regimen. The findings of the study indicated that genetic polymorphisms significantly impacted the antiemetic properties of granisetron, particularly due to variant CYP3A4 enzyme activity. The study also underscored the importance of leveraging CYP2D6-specific 5-HT3 receptor antagonists, such as dolasetron and tropisetron, to enhance therapy, particularly in Chinese patients (Lua et al., 2012).

In 2012, a cross-sectional study by Lua et al. was conducted in two public hospitals in northeastern Malaysia to determine the incidence of CINV with antiemetic use and assess its impact on patients' QOL. The study's participants were predominantly of Malaysian ethnicity (92.7%), with a mean age of 49.1 ± 9.6. The majority of patients had stage III cancer and received moderately emetogenic chemotherapy. The study found that a majority of patients experienced nausea (90.2%) and vomiting (29.3%) during or after chemotherapy. Patients who received granisetron, a 5-HT3 receptor antagonist, for two consecutive days reported the drug to be "somewhat useful" (97.6%). Conversely, patients who received a combination of granisetron and corticosteroid (dexamethasone) for four days and experienced CINV rated the experience as "severe." A notable correlation was identified between the presence of moderate to severe nausea and fatigue. Furthermore, patients who experienced vomiting demonstrated worse health-related QOL compared to those who did not (Lua et al., 2012).

A cross-sectional study was conducted at Hospital Melaka in Malaysia, with the objective of investigating the impact of chemotherapy on the quality of life (QOL) of patients diagnosed with breast cancer. The study also examined the influence of confounding variables, including patient age, the stage of cancer, and the presence of comorbidities such as nausea, vomiting, diarrhea, and anorexia. The study population comprised 32 female patients (mean age: 49.7 years) who were administered the FEC regimen. The study found that 46.8% of the patients had stages III and IV of the disease, while approximately half had early-stage breast cancer. The EORTC QLQ-C30 questionnaire was utilized to assess patients' quality of life both prior to and following treatment. The study revealed a substantial decline in QOL following chemotherapy, accompanied by elevated rates of adverse effects, including nausea, vomiting, loss of appetite, and diarrhea. The authors concluded that chemotherapy significantly diminished the QOL of breast cancer patients due to these side effects, emphasizing the need for interventions to improve QOL (Chee Chean et al., 2016).

A similar study by Yusuf et al. included 76 breast cancer patients, predominantly Malays (76.3%) and Chinese (19.7%), in Kelantan, Malaysia. The majority of patients were younger than 50 years old and had advanced-stage breast cancer (31% Stage III and 37.9% Stage IV). The study employed the EORTC QLQ-C30 and QLQ-BR23 questionnaires to assess patients' QOL. While both Malay and Chinese patients exhibited satisfactory QOL, Malay women exhibited comparatively lower QOL scores, attributable to a

higher prevalence of prevalent symptoms such as nausea and vomiting, dyspnea, and constipation (Yusuf et al., 2013).

Noor et al. conducted semi-structured interviews with sixteen breast cancer patients receiving chemotherapy as part of a qualitative descriptive study. The objective of this research was to examine how CINV affects patients' quality of life. A significant proportion of the patient population was in the early stages of the disease and had recently received a breast cancer diagnosis (84.6%). The study found that all patients experienced varying degrees of acute and delayed CINV, which had a negative impact on their eating patterns and daily life activities. The authors underscored the critical nature of CINV, emphasizing its deleterious impact on the QOL of breast cancer patients and underscoring the need for further investigation to elucidate its mechanisms and develop effective mitigation strategies (Lua et al., 2016).

In 2016, a study involving 223 Malaysian breast cancer patients from diverse ethnic backgrounds (Malay, Chinese, Indian, and others) evaluated QOL using the EORTC QLQ-C30 and QLQ-BR23 questionnaires. The majority of patients were diagnosed with advanced-stage disease (Stage III and IV) with a mean age of 52.4 years. Patients aged 50 years and above exhibited enhanced QOL, characterized by a reduced prevalence of specific symptoms, including nausea and vomiting, diarrhea, constipation, and alopecia, resulting from systemic therapy. The study highlighted the detrimental impact of nausea and vomiting on patients' QOL during chemotherapy (Ganesh et al., 2016).

Genetic Effects on Chemotherapy-Induced Nausea and Vomiting

Pharmacokinetic and pharmacodynamic differences are therapeutically significant due to individual variations in drug metabolism, which are impacted by both heredity and exogenous factors, including the environment, nutrition, and concurrent drug therapy (Gross et al., 1999; Ruzilawati et al., 2007). Significant alterations in medication metabolism are predominantly attributable to alterations in cytochrome P450 (CYP) enzymes. The CYP3A subfamily, comprising CYP3A4, CYP3A5, CYP3A7, and CYP3A47, is responsible for over 50% of the drug metabolisms in clinical use. The variations in CYP3A4 activity can be attributed to different CYP3A4 alleles (Ruzilawati et al., 2007). The metabolism of 5-HT3 receptor antagonists, such as dolasetron and tropisetron, is predominantly associated with the CYP2D6 subgroup. In contrast, granisetron is metabolized by the CYP3A43 subgroup, while ondansetron is metabolized by CYP2D6, CYP1A2, CYP3A4, and CYP2E1. Notwithstanding, 5-HT3 receptor antagonists demonstrate a suboptimal response in a substantial proportion of cancer patients. A significant factor contributing to interindividual variations in medication pharmacological reactions is genetic polymorphisms in enzymes, such as the hepatic cytochrome P-450 enzyme subfamily (Kaiser et al., 2002).

A recent longitudinal prospective observational study was conducted in Malaysia among breast cancer patients to elucidate the effect of genetic polymorphism, specifically in CYP3A4, on the antiemetic efficacy of granisetron across the three major ethnic groups (Malay, Chinese, and Indian). Patients were closely monitored for the incidence of nausea and vomiting during the initial 24 hours of chemotherapy administration and subsequently 3 to 5 days later. The majority of the patients were of Chinese descent (63.9%) and had breast cancer in its early stages (79.7%). The treatment regimens employed included FEC (93%), CAF (3.8%), and CMF (3.2%). Prior to the administration of any pharmaceutical agent to a patient, a 5-HT3 antagonist (granisetron) and dexamethasone were administered. Following treatment, metoclopramide and dexamethasone were administered. Acute and delayed CINV occurred in 45 Chinese individuals, but the Malay patients exhibited a reduced incidence of CINV. The study's findings underscore the potential of CYP3A4 mutations to influence the antiemetic efficacy of granisetron, offering a novel perspective on the influence of ethnicity on CINV management. To mitigate the occurrence of CINV, the study recommended that Chinese breast cancer patients opt for 5-HT3 receptor antagonists, such as tropisetron and dolasetron, given their primary metabolic processing via CYP2D6 (Hassan & Yusoff, 2011).

Conclusion

This review underscores the persistent challenges associated with chemotherapy-induced nausea and vomiting (CINV) among breast cancer patients in Malaysia, with its deleterious impact on their quality of life. Addressing this issue necessitates the adaptation of antiemetic treatment protocols to account for genetic variations among the country's multiethnic population. Malaysian healthcare providers are strongly encouraged to adopt patient-centered approaches that incorporate pharmacogenetic testing to optimize antiemetic therapies, ensuring more effective management of CINV. Furthermore, the enhancement of healthcare infrastructure is imperative, involving the augmentation of access to supportive care services, the dissemination of patient education on CINV management, and the promotion of adherence to evidence-based guidelines. Future research should concentrate on identifying specific barriers to care and developing targeted interventions to improve outcomes for breast cancer patients.

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Case Report

Papillary Tumor of Pineal Region; A Case Report

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Abstract

Background: *Papillary tumor of the pineal region (PTPR) is a rare neuroepithelial tumor that was first classified by the World Health Organization (WHO) in 2003. The diagnosis of this tumor is challenging due to its imaging features, which overlap with those of other pineal region tumors, and due to the paucity of pediatric cases reported in the literature.*

Case Presentation: *We present the case of a 4-year-old male patient who exhibited symptoms including progressive headaches, vomiting, and neurological deficits, such as upward gaze palsy and ataxia. Imaging revealed a pineal mass causing obstructive hydrocephalus, initially suspected to be germinoma. Following the placement of a ventriculoperitoneal shunt, the patient underwent gross total resection (GTR) of the tumor through a posterior fossa approach. Histopathological analysis confirmed PTPR (WHO grade 2/3), with papillary structures and immunohistochemical positivity for S100 and CD56. The patient received adjuvant radiotherapy to the surgical cavity (54 Gy in 1.8 Gy fractions), and no recurrence or neurological deficits were observed at the 6-month follow-up.*

Discussion: *PTPR presents significant diagnostic and therapeutic challenges due to its nonspecific imaging features and critical anatomical location. GTR remains the primary treatment modality, often necessitating adjuvant radiotherapy to reduce the risk of recurrence. This case underscores the significance of multidisciplinary approaches and meticulous radiotherapy planning, particularly in pediatric patients, in achieving a balance between benefits and neurocognitive functions.*

Conclusion: *This report underscores the necessity of considering PTPR in pediatric pineal masses and demonstrates that early diagnosis, surgical resection, and adjuvant radiotherapy can result in improved outcomes. Given the low five-year disease-free survival rate, regular and frequent follow-ups are crucial, with careful attention to every sign, symptom, and imaging change.*

Keywords: *Pediatric CNS, Pineal Tumor, Papillary Tumor of Pineal Region, Pineal Region, Neuro-Oncology.*

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Introduction

Pineal region tumors are considered surgically challenging due to their deep location within the brain, which complicates access, and their proximity to critical neurovascular structures, such as the deep cerebral veins and dorsal midbrain. These challenges are further compounded in pediatric patients. Given the broad spectrum of tumors that can arise in this region, surgical resection or tissue sampling is imperative for precise diagnosis, as different tumor types have distinct prognoses and treatment strategies (Favero et al., 2021).

Papillary tumor of the pineal region (PTPR) is a rare and distinct neuroepithelial tumor that was first introduced into the World Health Organization (WHO) classification of central nervous system (CNS) tumors in 2003 (Jouvet et al., 2003). Prior to its inclusion in the aforementioned classification, it was described under various other tumor categories, including papillary pineocytoma, choroid plexus tumor, meningioma, and ependymoma. PTPR exhibits distinctive histological and immunohistochemical features, distinguishing it from other pineal region tumors. While it is most prevalent in adults, the age range is wide, spanning from 5 to 66 years, with a mean age of 31.5 years, as reported by Fèvre-Montange et al. (2006).

The clinical presentation of PTPR is associated with mass effect on adjacent structures. The most prevalent presentation (accounting for up to 80% of cases) is obstructive hydrocephalus, resulting from compression of the cerebral aqueduct. This leads to symptoms of elevated intracranial pressure, including headache, nausea, vomiting, and papilledema. Other presentations include long-term visual disturbances resulting from tectal plate or colliculus compression and Parinaud syndrome (Poulgrain et al., 2011; Ribeiro et al., 2018; Shakir et al., 2015a). Radiological findings typically include a well-defined, contrast-enhancing mass on MRI, an appearance shared by many other tumors in the area, including other pineal tumors, ependymal tumors, germ cell tumors, and metastatic carcinomas. Given the heterogeneity in management of these tumors, a histopathological confirmation is necessary for diagnosis (Chang et al., 2008; Ribeiro et al., 2018). Immunohistochemical analysis frequently reveals positivity for markers such as keratin (CK), epithelial membrane antigen (EMA), and S100 protein, which are critical diagnostic indicators for PTPR (Hasselblatt et al., 2006; Kuchelmeister et al., 2006).

Gross total resection (GTR) is the optimal approach for achieving symptom relief and long-term disease control. However, complete resection may present a challenge in pediatric patients due to the proximity of the tumor to critical structures, such as the vein of Galen and the quadrigeminal plate (Azab et al., 2014; Dagnew et al., 2007). In circumstances where GTR is not feasible, subtotal resection (STR) is often accompanied by adjuvant radiotherapy to mitigate the probability of recurrence (Dagnew et al., 2007; Fèvre-Montange et al., 2006; Yamaki et al., 2019a). The role of adjuvant radiotherapy after GTR remains to be delineated; however, given the high recurrence rate, it is probable that the majority of patients will undergo radiotherapy postoperatively (Lancia et al., 2020). However, the utilization of radiotherapy in pediatric patients necessitates a meticulous approach, with the objective of mitigating the potential for long-term consequences on neurocognitive function and developmental outcomes (Major et al., 2022).

While PTPR generally carries an intermediate prognosis, recurrence is not uncommon, particularly in cases of incomplete resection. The 5-year overall survival and progression-free survival rates are estimated to be 73% and 27%, respectively (Fèvre-Montange et al., 2006).

This report presents a case of PTPR in a pediatric patient, emphasizing the unique challenges in clinical management and reviewing available literature on outcomes and therapeutic strategies in the pediatric population.

Case Presentation

History

A 5-year-old male patient exhibited symptoms including progressive headaches, generalized weakness, poor appetite, and vomiting over a period of one month, accompanied by neurological findings such as impaired upward gaze, nystagmus, and ataxia.

Imaging Findings

A CT scan performed at the emergency department following the patient's clinical deterioration revealed a 30 * 20 mm well-defined, heterogenous pineal region mass with engulfed calcification, causing dilatation of the third and lateral ventricles, suggesting pineal germinoma.

Contrast-enhanced MRI (**Figure 1**) revealed a 30 * 20 * 23 mm mass at the pineal region, iso-intense in T1, T2, and FLAIR sequences, restricted in diffusion, and vividly enhancing post-contrast, resulting in moderate hydrocephalus in the third and lateral ventricles with periventricular effusion. These findings are consistent with a diagnosis of pineal germinoma. A comprehensive neuraxis MRI revealed no additional lesions.

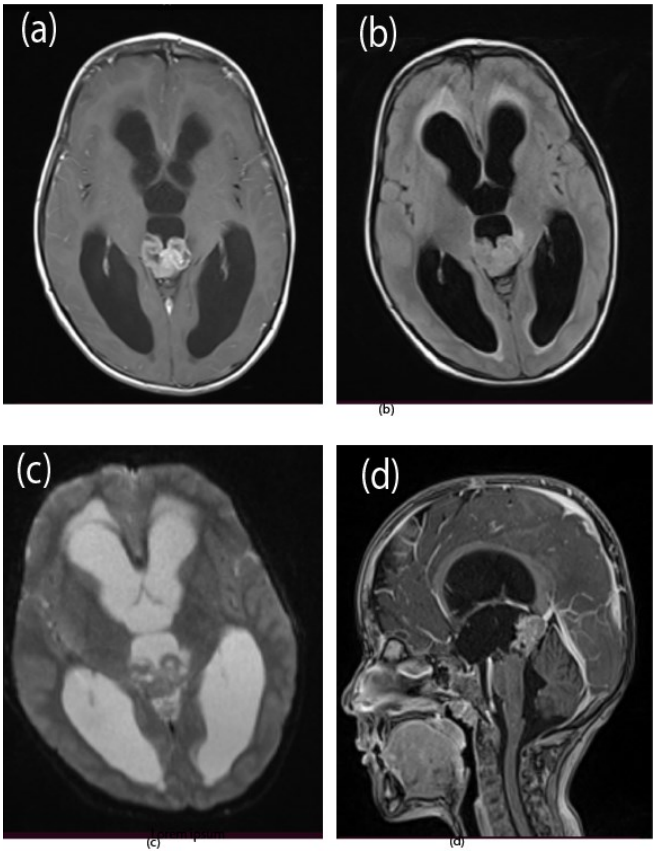

Figure 1. Pre-Operative MRI, (a): T1 Post Contrast, (b) FLAIR, (c) Diffusion Weighted Series, (d) Sagittal View T1 Post Contrast.

Surgical Intervention

Subsequent to the imaging diagnosis, the patient underwent ventriculoperitoneal shunt placement surgery to alleviate the hydrocephalus. Once the patient's condition stabilized, he underwent laboratory investigations focusing on germ cell tumor markers. All the panels returned to normal, including the tumor markers and CSF cytology.

Following further neurosurgical consultations and extensive discussion in MDT, the decision was made to proceed with open surgery aiming for GTR. The surgical procedure was performed via an incision in the midline of the posterior fossa, with the dura opened through a left infratentorial suprasellar approach, and the tumor was completely excised.

Postoperative Course

The patient exhibited a smooth postoperative recovery, regaining the majority of his basic activities by the tenth day after the operation. A post-operative MRI revealed the absence of the pineal gland and the absence of a space-occupying lesion. The patient also had a ventriculoperitoneal shunt placed in the right lateral ventricle, with the tip positioned in the ventral horn.

Histopathological Examination

A histopathological examination was conducted, which revealed the following findings:

Due to the absence of stereotactic biopsy and the tumor location, the preoperative biopsy was not performed. The initial histopathological report indicated the presence of multiple papillary structures lined by multiple layers of cuboidal cells, moderate nuclear atypia, scattered mitoses, and foci of necrosis. No microvascular proliferation was observed. Subsequent immunohistochemistry panel testing revealed strong diffuse positivity for S100 and CD56, along with punctate positivity for AE1/3. Conversely, GFAP, PLAP, OCT 3/4, chromogranin, and synaptophysin were negative. Ki-67 labeling index revealed an approximate value of 15-20%. These findings collectively indicate a diagnosis of papillary tumor of the pineal region, classified as World Health Organization (WHO) grade 2-3.

To ensure the accuracy of the diagnosis, a second opinion was sought from an independent laboratory. This second evaluation involved a review of both slides and a repetition of the IHC panel. The results of this second evaluation were consistent with those of the initial evaluation, confirming the initial diagnosis.

Radiotherapy

The patient was scheduled to receive postoperative adjuvant radiotherapy. One month after surgery, he underwent conventional external beam radiotherapy (EBRT). The treatment was simulated in a supine position with thermoplastic mask fixation. A CT series with 2.5 mm slice thickness was acquired, and the target volume was delineated as the surgical cavity on fused MRI series with the addition of 1.0 cm extra margin, constrained by anatomical barriers. The prescribed dose was 54 Gy in 1.8 Gy daily fractions. The planning was performed utilizing a full-arc VMAT technique. Special attention was given to organs at risk, including both hippocampi. The radiation treatment course proceeded without incident, with the exception of acute toxicity manifested as nausea. This adverse effect was addressed through the administration of a short-term corticosteroid. Concurrent or adjuvant chemotherapy was not offered.

The patient has been under follow-up since the completion of radiotherapy, with MRI imaging conducted periodically (**Figure 2**). After eight months of treatment, no recurrence or abnormal MRI signals were observed, and the patient was found to be fully active with no neurological abnormalities.

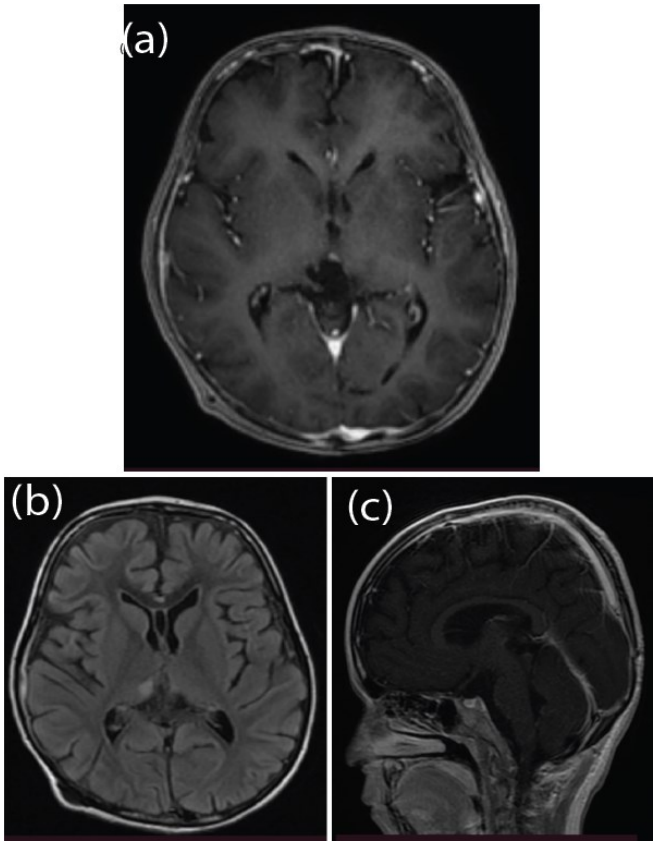

Figure 2. Eight Months Post Treatment MRI; (a) T1 Post-Contrast, (b) FLAIR, (c) Sagittal T1 Post-Contrast

Discussion

PTPR, being an uncommon neoplasm, poses a considerable diagnostic challenge due to its location, as it can be mistaken for more prevalent pediatric brain neoplasms, particularly central nervous system germinomas. In such cases, surgical intervention is often limited to diagnostic biopsy, with chemotherapy and radiotherapy serving as the primary treatment approaches (Osorio & Allen, 2015). The absence of unique imaging characteristics that distinguish PTPR from other tumors in the region poses a significant diagnostic challenge. Its variable T1 and T2 enhancement patterns have been observed to overlap with those of several other tumors, including germinomas, ependymomas, pineal parenchymal tumors, and metastases (Chang et al., 2008; Ribeiro et al., 2018; Smith et al., 2010; Vandergriff et al., 2012).

Despite the tumor's radiological resemblance to germ cell tumors, open surgery was opted for with the aim of achieving gross total excision. This approach was justified by the following factors: the tumor's unicentric and respectable nature, negative germ cell tumor markers, a neuraxis MRI showing no abnormalities, and the inaccessibility of stereotactic biopsy. It is widely acknowledged that complete surgical removal is the most significant prognostic factor and is associated with enhanced disease-free survival. Other prognostic features include the tumor size and mitotic index (represented by Ki-67) (Heim et al., 2014; Mobark et al., 2022; Yamaki et al., 2019b).

Given the high recurrence rate associated with PTPR, the recommendation is often for adjuvant radiotherapy, even after GTR (Lancia et al., 2020). However, the existing body of literature does not provide sufficient data to determine the most appropriate radiotherapy technique or modality. Conventionally, fractionated radiotherapy, stereotactic radiosurgery, and stereotactic radiotherapy are all employed in extant literature. The treatment volumes also vary, encompassing local, whole ventricular, whole cranial, and craniospinal irradiation (Edson et al., 2015; Fauchon et al., 2013; Kim et al., 2010; Shakir et al., 2015b). A notable study by Fèvre-Montange et al. (2006) reported a mean survival of 57.4 months for patients undergoing conventionally fractionated EBRT for resected PTPR cases, with most patients experiencing recurrence within five years. In this particular instance, the patient underwent external beam radiotherapy (EBRT) to the surgical bed with 1 cm expansion for the CTV, constrained by anatomical barriers. Meticulous attention was paid to organs at risk, including the hippocampi, to minimize long-term neurocognitive sequelae. The total dose of 54 Gy was administered in 1.8 Gy fractions. The absence of data concerning the benefits of larger treatment volumes and the potential neurocognitive toxicity associated with them, particularly in this age group, justified the utilization of the aforementioned treatment technique. It is noteworthy that no concurrent chemotherapy was administered in this case, due to the limited efficacy of chemotherapy in PTPR (Fauchon et al., 2013; West et al., 2015).

The study's limitations include its relatively brief follow-up period, and the absence of long-term neurocognitive assessments related to surgical and radiation interventions. We intend to continue monitoring the case and present updates in future reports.

Conclusion

Papillary tumor of the pineal region (PTPR) poses significant diagnostic and therapeutic challenges, particularly in pediatric patients. Gross total resection (GTR) is paramount for enhancing prognosis, while adjuvant radiotherapy is frequently imperative due to the tumor's high recurrence rate. This case underscores the necessity for meticulous surgical and radiotherapy planning to optimize tumor control while minimizing neurocognitive risks, particularly in younger patients. While the short-term prognosis appears favorable, it is imperative to emphasize the necessity of regular and frequent follow-ups, with meticulous observation of every sign, symptom, and imaging change, given the relatively low five-year disease-free survival rate.

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